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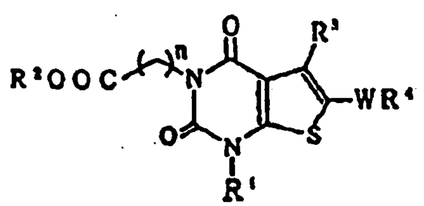

(I')

(57) Abstract

A thienopyrimidine derivative, wherein it has: (1) a carboxyl group which may be esterified and (2) a group which is capable of forming an anion or a group convertible thereinto except carboxyl group in its molecule, such as a compound of formula (I'), wherein each of R^1 and R^2 are hydrogen or an optionally substituted hydrocarbon residue, R^3 is a C_{1-6} alkyl group which is substituted by a C_{1-6} alkoxy-carbonyl group or a group of the formula: $-NH-SO_2-R^5$, wherein R^5 is : (1) a C_{1-6} alkyl group which may optionally be substituted by halogen or (2) a C_{6-14} aryl group, R^4 is an optionally substituted hydrocarbon residue or an optionnally substituted heterocyclic group, W denotes a chemical bond or a spacer group and n denotes an integer of 1 to 3; or a salt thereof, exhibits high endothelin receptor antagonist action and can, therefore, be used with advantager as a prophylactic or therapeutic drug for acute renal failure, myocardial infarction, lever disorder, angina pectoris, cerebral infarction, cerebrovasospasm, hypertension, kidney disease, asthma, ectopic angina, Raynaud's syndrome, pulmonary hypertension, surgical shock, chronic heart failure, atherosclerosis, cardiac hyperthrophy, migraine, etc., as a prophylactic or therapeutic drug for organ surgery- or graft-associated hypofunction of organs, as a prophylactic drug for vascular restenosis following percutaneous transluminal coronary angioplasty (PTCA), or as an inhibitor for vasoconstriction of cerebrovascular system or pulmonary vascular system.

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DESCRIPTION

THIENOPYRIMIDINE DERIVATIVES, THEIR PRODUCTION AND USE

Technical Field

The present invention relates to thienopyrimidine derivatives and salts thereof. The present invention further relates to methods for manufacturing the thienopyrimidine derivatives and the salts thereof, and pharmaceutical compositions containing the thienopyrimidine derivatives.

Background Art

The possibility has been suggested that, among adult diseases which are being encountered with increasing frequencies in these years, ischemia-associated diseases such as cerebral infarction, angina pectoris, myocardial infarction, renal failure and hepatic disorder are mediated by endothelin. Endothelin is a peptide of 21 amino acid residues as produced and released from endothelial cells and endothelin-1, endothelin-2 and endothelin-3 have so far been identified. Throughout this specification, these endothelin species are collectively referred to as "endothelin".

Endothelin reportedly is a substance having the most potent and lasting vasoconstrictive, pressor and heart muscle contractility-increasing actions of all the physiological substances and synthetic substances so far known. It is suspected that these actions of this particular peptide are manifested through the endothelin receptors suspected to exist in the vascular smooth muscle fascia and elsewhere. As the endothelin receptors, endothelin-A and endothelin-B receptors (both are collectively referred to as endothelin receptors) are already known.

Therefore, any compound having an affinity for the endothelin receptors and showing endothelin antagonizing activity is likely to be effective in the prevention and treatment of ischemia-associated diseases (for example, cerebral infarction, angina pectoris, myocardial infarction, renal failure, and hepatic disorder) and the development of a drug of this type has been awaited in earnest. As synthetic compounds having endothelin receptor antagonist activity, the compounds described typically in EP-A-510526, EP-A-526708, PCT•WO-9308799, and Journal of Medicinal Chemistry, 37, 1553-1557, 1994 are known.

Recently, it has been pointed out that a thieno-pyrimidine derivative has endothelin receptor antagonist activity (European Patent Publication No. 640,606).

During the study of thienopyrimidine compounds, the present inventors have found that a thienopyrimidine compound which has a carboxyl group and a group capable of forming an anion in the molecule has particularly potent endothelin receptor antagonist activity. The inventors did further research on the basis of the above finding and have completed the present invention.

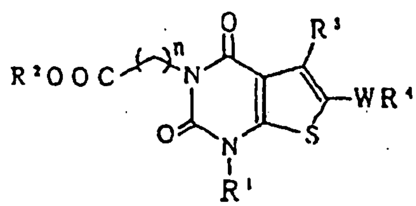
Disclosure of Invention

The present invention provides:

(1) A thieno[2,3-d]pyrimidine derivative, i.e. compound (I), wherein it has (i) a carboxyl group or an ester thereof and (ii) a group other than a carboxyl group which is capable of forming an anion or a group convertible thereinto in its molecule;

(2) A compound according to the item (1), wherein the group other than a carboxyl group which is capable of forming an anion or a group convertible thereinto is tetrazolyl, an optionally substituted sulfonamido

group, a phosphono group or a sulfo group, each of which may optionally be substituted by alkyl or acyl;
(3) A compound (I') of the formula:



(I')

wherein each of R^1 and R^2 are hydrogen or an optionally substituted hydrocarbon residue, R^3 is a C_{1-6} alkyl group which is substituted by a C_{1-6} alkoxy-carbonyl group or a group of the formula: $-NH-SO_2-R^5$ wherein R^5 is (1) a C_{1-6} alkyl group which may optionally be substituted by halogen or (2) a C_{6-14} aryl group, R^4 is an optionally substituted hydrocarbon residue or an optionally substituted heterocyclic group, W denotes a chemical bond or a spacer group and n denotes an integer of 1 to 3, or a salt thereof;
(4) A compound according to the item (3), wherein R^1 is an optionally substituted C_{1-20} hydrocarbon residue;
(5) A compound according to the item (4), wherein the C_{1-20} hydrocarbon residue is a C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{2-10} alkenyl, C_{6-14} aryl or C_{7-20} aralkyl group;
(6). A compound according to the item (4), wherein R^1 is an optionally substituted C_{7-20} aralkyl group;
(7) A compound according to the item (3), wherein R^1 is a hydrocarbon residue optionally substituted with (1) halogen, (2) nitro, (3) cyano, (4) an optionally substituted hydroxyl group, (5) a group of the formula: $-S(O)f-R^6$, wherein f denotes an integer of 0 to 2, and R^6 is a hydrogen atom or an optionally substituted hydrocarbon residue, (6) an optionally substituted amino group or (7) an optionally substituted 5- or 6-membered heterocyclic group which contains 1 to 4

heteroatom(s) of oxygen, sulfur or nitrogen;

(8) A compound according to the item (3), wherein R^1 is a hydrocarbon residue optionally substituted with halogen or a C_{1-4} alkylthio group;

(9) A compound according to the item (3), wherein R^2 is an optionally substitueted C_{1-20} hydrocarbon residue;

(10) A compound according to the item (9), wherein R^2 is an optionally substituted C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{2-10} alkenyl, C_{6-14} aryl or C_{7-20} aralkyl group;

(11) A compound according to the item (3), wherein R^2 is an optionally substituted C_{1-10} alkyl;

(12) A compound according to the item (3), wherein R^7 is a hydrocarbon residue optionally substituted with (1) halogen, (2) nitro, (3) cyano, (4) an optionally substituted hydroxyl group, (5) a group of the formula: $-S(O)f-R^6$, wherein f denotes an integer of 0 to 2, and R^6 is a hydrogen atom or an optionally substituted hydrocarbon residue, (6) an optionally substituted amino group or (7) an optionally substituted 5- or 6-membered heterocyclic group which contains 1 to 4 heteroatom(s) of oxygen, sulfur or nitrogen;

(13) A compound according to the item (3), wherein R^7 is a hydrocarbon residue optionally substituted with (1) halogen, (2) nitro, (3) hydroxyl, (4) cyano, (5) C_{1-4} alkylthio, (6) C_{1-4} alkoxy, (7) C_{1-6} alkyl-carbonyloxy or (8) C_{3-6} cycloalkyl-oxycarbonyloxy;

(14) A compound according to the item (3), wherein R^2 is hydrogen or a C_{1-6} alkyl group which may optionally be substituted by C_{1-6} alkyl-carbonyloxy or C_{3-6} cycloalkyl-oxycarbonyloxy;

(15) A compound according to the item (3), wherein R^1 is a C_{1-6} alkyl group which is substituted by a C_{1-6} alkoxy-carbonyl group or a group of the formula: $-NH-SO_2-R^{5'}$, wherein $R^{5'}$ is a C_{1-6} alkyl group or a C_{6-14} aryl

group;

(16) A compound according to the item (3), wherein R^3 is a C_{1-6} alkyl group which is substituted by a group of the formula: $-NH-SO_2-R^5$, wherein R^5 is (1) a C_{1-6} alkyl group which may optionally be substituted by halogen or (2) a C_{6-14} aryl group;

(17) A compound according to the item (3), wherein R^3 is a C_{1-6} alkyl group which is substituted by a group of the formula: $-NH-SO_2-R^{5'}$, wherein $R^{5'}$ is a C_{1-6} alkyl group or a C_{6-14} aryl group;

(18) A compound according to the item (3), wherein R^4 is optionally substituted C_{1-20} hydrocarbon residue or an optionally substituted 5- to 13-membered heterocyclic group which contains 1 to 4 heteroatom(s) of oxygen, sulfur or nitrogen;

(19) A compound according to the item (3), wherein R^4 is an optionally substituted C_{6-14} aryl group;

~~(20) A compound according to the item (3), wherein~~ $\cancel{R^4}$ is a hydrocarbon residue optionally substituted with (1) halogen, (2) nitro, (3) cyano, (4) C_{1-6} alkoxy which may optionally be substituted by C_{1-6} alkoxy, carboxyl, halogen, C_{1-6} alkyl-carbamoyl or 5 to 7 membered nitrogen-containing heterocyclic group-carbonyl, (5) C_{7-13} aralkyloxy, (6) C_{1-4} alkyl which may be substituted by C_{1-3} alkoxy, (7) C_{1-6} alkanoyl, (8) C_{1-4} alkylthio, (9) C_{2-6} alkenyloxy, (10) C_{1-6} alkoxy-carbonyl or (11) C_{1-6} alkyl-carbamoyl;

(21) A compound according to the item (3), wherein the R^4 is a hydrocarbon residue optionally substituted with C_{1-6} alkoxy which may optionally be substituted by C_{1-6} alkoxy, carboxyl, halogen, C_{1-6} alkyl-carbamoyl, a 5 to 7 membered nitrogen-containing heterocyclic group-carbonyl;

(22) A compound according to the item (3), wherein W is

a spacer group selected from the group consisting of (1) C_{1-4} alkylene, (2) C_{2-6} alkenylene, (3) a group of the formula $-(CH_2)cNR^7-$, where c represents an integer of 0-3, R^7 represents hydrogen or C_{1-6} alkyl, (4) -CO-, (5) a group of the formula $-CONR^7-$, where R^7 is as defined above, (6) -O-, (7) a group of the formula: -S(O)f-, where f represents an integer of 0 to 2, and (8) a group of the formula: $-NR^7S(O)e-$, where e represents an integer of 0-2; R^7 is as defined above;

(23) A compound according to the item (3), wherein W is a chemical bond;

(24) A compound according to the item (3), wherein R^1 is benzyl group which may optionally be substituted by (1) halogen or (2) C_{1-4} alkylthio,
R^2 is a hydrogen atom or a C_{1-4} alkyl group which may optionally be substituted by (1) C_{1-6} alkyl-carbonyloxy or (2) C_{3-6} cycloalkyl-oxycarbonyloxy,
R^3 is a C_{1-6} alkyl group which is substituted by (1) a C_{1-6} alkoxy-carbonyl group or (2) a group of the formula: $-NH-SO_2-R^{5''}$ (wherein $R^{5''}$ is (1) a C_{1-3} alkyl group which may optionally be substituted by halogen or (2) a phenyl group, W is a chemical bond,
R^4 is a phenyl group which is substituted by (1) C_{1-4} alkoxy, which may be substituted by C_{1-6} alkoxy, carboxyl, C_{1-6} alkyl-carbamoyl, piperazinecarbonyl or halogen, (2) C_{7-8} aralkyloxy, (3) C_{1-4} alkyl which may be substituted by C_{1-3} alkoxy, (4) C_{1-6} alkanoyl, (5) C_{2-4} alkenyloxy, (6) C_{1-6} alkoxy-carbonyl or (7) C_{1-6} alkyl carbamoyl;

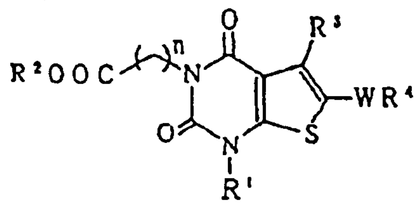
(25) 2,4(1H,3H)-dioxo-6-(4-methoxymethoxyphenyl)-1-(2-methylthiobenzyl)-5-(methanesulfonamidomethyl)-thieno[2,3-d]pyrimidine-3-acetic acid or its salt;

(26) 2,4(1H,3H)-dioxo-6-(4-methoxymethoxyphenyl)-1-(2-methylthiobenzyl)-5-(ethanesulfonamidomethyl)-thieno[2,3-d]pyrimidine-3-acetic acid or its salt;

(27) 2,4(1H,3H)-dioxo-6-(4-methoxyphenyl)-1-(2-methylthiobenzyl)-5-(methanesulfonamidomethyl)-thieno[2,3-d]pyrimidine-3-acetic acid or its salt;

(28) Ethyl 2,4(1H,3H)-dioxo-6-(4-methoxyphenyl)-1-(2-methylthiobenzyl)-5-(carboxymethyl)thieno[2,3-d]pyrimidine-3-acetate;

(29) A method for producing a compound as defined in the item (3), which comprises subjecting a compound (II) of the formula:



(II)

wherein, R^1, R^2, W and R^4 have the same meaning as defined in the item (3) and $R^{3'}$ is a C_{1-6} alkyl group which is halogenated or cyanated, to (1) a nucleophilic substitution reaction with a sulfonamide compound when the alkyl of $R^{3'}$ is halogenated or (2) alkali-hydrolysis and then esterification when the alkyl of $R^{3'}$ is cyanated;

(30) A pharmaceutical composition, which comprises a compound as defined in the item (1), (3) or (28) and a carrier, excipient or diluent therefor;

(31) A pharmaceutical composition according to the item (30), which is a therapeutic drug for treating vasoconstriction in a mammal;

(32) A pharmaceutical composition according to the item (31), wherein the vasoconstriction is in a coronary artery, coronary vein, cerebrovascular system or pulmonary vascular system; and

(33) A pharmaceutical composition according to the item (30), which is for antagonizing endothelin activity;

(34) A pharmaceutical composition according to the item (33), which is a therapeutic drug for acute renal insufficiency, cardiac infarction or liver

insufficiency;

(35) A pharmaceutical composition according to the item (33), which is a treapeutic drug for hypofunction of an organ caused by a surgery or transplant;

(36) A pharmaceutical composition according to the item (35), wherein the organ is liver;

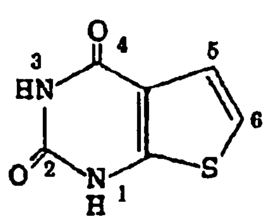
(37) A method for treating a mammal suffering from vasoconstriction, which comprises administering an effective amount of a compound as defined in the item (1), (3) or (28) to the mammal; and

(38) A method for treating a mammal suffering from acute renal insufficiency, cardiac infarction or liver insufficiency, which comprises administering an effective amount of a compound as defined in the item (1), (3) or (28) to the mammal.

(39) Use of a compound as defined in item (1), (3) or (28) for producing a pharmaceutical composition for the manufacture of a medicament for therapeutic application on vasoconstriction.

(40) Use of a compound as defined in item (1), (3) or (28) for producing a pharmaceutical composition for the manufacture of a medicament for therapeutic application on acute renal insufficiency, cardiac infarction or liver insufficiency.

The nucleus of the present compound, 2,4(1H,3H)-dioxo-thieno[2,3-d]pyrimidine, is shown below:

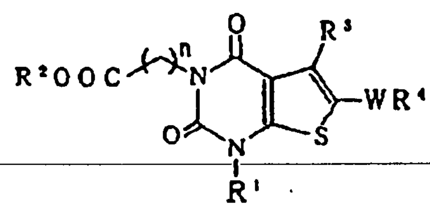


The esterified carboxyl group in the thienopyrimidine derivatives includes a group represented by the formula: -CO-D, wherein D denotes (1) hydroxyl group, (2) a group of the formula: $-O-R^8$,

wherein R^8 is an optionally substituted hydrocarbon residue or an optionally substituted amino group.

The group which is capable of forming an anion or a group convertible thereinto except carboxyl group includes tetrazolyl, an optionally substituted sulfonamide group, e.g. a group of the formula: $-NH-SO_2-R^5$ wherein R^5 is (1) a C_{1-6} alkyl group which may optionally be substituted by halogen or (2) a C_{6-14} aryl group, phosphono group and sulfo group, each of which may optionally be substituted by one or 2 of C_{1-6} alkyl or acyl, e.g. C_{2-5} alkanoyl, e.g. acetyl, propionyl, butyryl, valeryl, or C_{6-14} arylcarbonyl, e.g. benzoyl.

As preferred example of the compound (I), mention is made of a compound (I') of the formula:



(I')

wherein each of R^1 and R^2 are hydrogen or an optionally substituted hydrocarbon residue, R^3 is a C_{1-6} alkyl group which is substituted by a C_{1-6} alkoxy-carbonyl group or a group of the formula: $-NH-SO_2-R^5$ wherein R^5 is (1) a C_{1-6} alkyl group which may optionally be substituted by halogen or (2) a C_{6-14} aryl group, R^4 is an optionally substituted hydrocarbon residue or an optionally substituted heterocyclic group, W denotes a chemical bond or a spacer group and n denotes an integer of 1 to 3, or a salt thereof.

The hydrocarbon residue in the optionally substituted hydrocarbon residue for the group R^8 in the group D, the group R^1, the group R^2, the group R^4 in the formula (I') and the group R^6 mentioned below includes a hydrocarbon residue having one to 20 carbon atoms. As examples of the C_{1-20} hydrocarbon residue, mention is

made of C_{1-10} alkyl, e.g. methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, t-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, etc, and among others, C_{1-6} alkyl is preferable, C_{3-10} cycloalkyl, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, etc, and among others, C_{3-6} cycloalkyl is preferable, C_{7-10} bicycloalkyl, e.g. bicyclo[2,2,1]heptyl, bicyclo[2,2,2]octyl, bicyclo[3,2,1]octyl, bicyclo[3,2,1]nonyl, bicyclo[4,2,1]nonyl and bicyclo[4,3,1]decyl, etc, C_{2-10} alkenyl, e.g. vinyl, allyl, isopropenyl, 1-butenyl, 2-butenyl, butadienyl, hexatrienyl, etc, and among others, C_{2-6} alkenyl is preferable, C_{6-14} aryl e.g. phenyl, naphthyl, anthryl, phenanthryl, acenaphthyl, anthracenyl, etc., among others, phenyl, 1-naphthyl, 2-naphthyl are preferable, and C_{7-20} aralkyl, e.g. benzyl, phenethyl, benzhydryl, trityl, etc, and among others, C_{7-8} aralkyl, e.g. benzyl and phenethyl are preferable.

The substituent which said hydrocarbon residue may optionally have includes but is not limited to (1) halogen, e.g. fluorine, chlorine, bromine, iodine, (2) nitro, (3) nitroso, (4) cyano, (5) hydroxyl group which may optionally be substituted by (i) C_{1-6} alkyl, which may optionally be substituted by hydroxyl, C_{1-6} alkoxy, C_{1-3}·alkoxy-C_{1-3} alkoxy, C_{1-3} alkylthio, oxy-C_{1-3} alkoxy, carboxyl, carbamoyl, C_{1-6} alkyl-carbamoyl, 5 to 7 membered nitrogen containing heterocyclic group-carbonyl or halogen, (ii) C_{1-6} acyl, (iii) C_{7-20} aralkyl, which may optionally be substituted by halogen, C_{1-3} alkoxy or C_{1-4} alkyl, (iv) C_{6-14} aryl, which may optionally be substituted by halogen, (v) C_{2-6} alkenyl, (vi) C_{3-7} cycloalkyl, (vii) C_{1-3} alkoxy-carbonyl, (viii) mono- or di-C_{1-6} alkyl-amino, (ix) C_{1-3} alkoxy-carbonyl, (x) C_{1-6} alkyl-carbonyl, (xi) C_{3-6} cycloalkyloxycarbonyl or (xii) trifluorosulfonyl, (6) a group of the formula:

-S(O)f-R^6, wherein f is an integer of 0 to 2, R^6 represents a hydrogen atom or a hydrocarbon residue which may optionally be substituted, the hydrocarbon residue has the same meaning as defined above, among others, C_{1-6} alkyl, C_{6-14} aryl, C_{7-20} aralkyl are preferable, and as examples of the substituent to the hydrocarbon residue, mention is made of halogen, nitro, cyano, hydroxy, oxo, thioxo, carboxyl, cyano-C_{6-14} aryl, halogeno-C_{6-14} aryl, etc, (7) an optionally substituted amino group, which is represented by the formula: -NR^9R^{10}, wherein each of R^9 and R^{10} are hydrogen, hydrocarbon residue, which has the same meaning as defined above, C_{1-6} acyl or a 5 to 13 membered heterocyclic group which is mentioned below, (8) an optionally substituted carboxyl group of the formula: -CO-R^{11} wherein R^{11} denotes (i) hydrogen, (ii) hydroxyl, (iii) C_{1-6} alkyl, (iv) C_{1-6} alkoxy, (v) C_{3-6} cycloalkyl, (vi) C_{6-14} aryl, (vii) C_{7-20} aralkyl, (viii) an optionally substituted amino group which is defined above or (vix) an optionally substituted 5- to 13-membered heterocyclic group which is mentioned below, (9) a 5- through 13-membered heterocyclic group containing 1-4 hetero-atom(s) selected from oxygen (O), sulfur (S) and nitrogen (N) as ring members, the heterocyclic group being optionally substituted by (i) halogen, (ii) C_{1-4} alkyl, (iii) C_{1-3} alkoxy, (iv) C_{1-4} alkylthio, (v) phenoxy which may optionally be substituted by a halogen,

(10) sulfo, (11) C_{6-14} aryl, e.g. phenyl, naphthyl, anthryl, phenanthryl, acenaphthyl, anthracenyl, etc, (12) C_{3-7} cycloalkyl, (13) C_{1-6} alkylenedioxy, e.g. methylenedioxy, ethylenedioxy, propylenedioxy, 2,2-dimethylenedioxy, etc, (14) oxo, (15) thioxo, (16) C_{2-4} alkenyl, (17) C_{3-4} alkynyl, e.g. propagyl, 2-butenyl, etc, (18) C_{3-10} cycloalkyl, (19) C_{2-10} alkenyl, e.g.

vinyl, allyl, isopropenyl, 1-butenyl, 2-butenyl, butadienyl, hexatrienyl, etc., and among others, C_{2-6} alkenyl is preferable, (20) C_{7-20} aralkyl, which has the same meaning as defined above, (21) amidino, and (22) azido.

When the hydrocarbon residue is cycloalkyl, cycloalkenyl, aryl or aralkyl, each of the group may have one to three of C_{1-6} alkyl, e.g. methyl, ethyl, propyl, isopropyl, butyl, as a substituent. The C_{1-6} alkyl group may further substituted by one to three of hydroxy, oxo, C_{1-3} alkoxy, e.g. methoxy, ethoxy, n-propoxy, isopropoxy, C_{1-3} alkylthio, halogen or carbamoyl.

The examples of the substituted alkyl, mention is made of (1) formyl, i.e. methyl is substituted by oxo, (2) carboxyl, i.e. methyl is substituted by oxo and hydroxy, (3) C_{1-6} alkoxy-carbonyl, i.e. methyl is substituted by oxo and alkoxy, e.g. methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, hydroxy-C_{1-6} alkyl, e.g. hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, (4) C_{1-3} alkoxy-C_{1-6} alkyl, e.g. methoxymethyl, ethoxyethyl, ethoxybutyl, propoxymethyl, propoxyhexyl.

In the above optionally substituted hydrocarbon residue, the number of the substituent(s) is preferably 1 to 6, more preferably 1 to 5, and still preferably 1 to 3 and most preferably 1 to 2. The number of the substituent(s) which is substituted on the substituent is preferably 1 to 3, more preferably 1 or 2.

In the formula (I), n denotes 1 to 3, preferably 1 or 2, more preferably 1.

The C_{1-6} alkyl group in the C_{1-6} alkyl group which is substituted by a C_{1-6} alkoxy-carbonyl group or a group of the formula: $-NH-SO_2-R^5$ mentioned for R^3 includes methyl, ethyl, n-propyl, isopropyl, n-butyl,

isobutyl, sec-butyl, t-butyl, pentyl, hexyl, etc. Particularly preferred is methyl or ethyl.

The C_{1-6} alkoxy in C_{1-6} alkoxy-carbonyl group of R^3 includes methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, isobutoxy, t-butoxy, pentoxy, hexyloxy. In particular, C_{1-4} alkoxy is preferable.

The C_{1-6} alkyl group of the C_{1-6} alkyl which may optionally be substituted by halogen of R^5 includes the same groups as mentioned above. In particular, methyl or ethyl, is preferred.

The halogen includes fluorine, chlorine, bromine, iodine. Among others, fluorine and chloride is preferable.

The number of the substituent is preferably 1 to 3.

The C_{6-14} aryl group of R^5 includes phenyl, naphthyl, anthryl. Among others, phenyl is preferable.

The heterocyclic group of the optionally substituted heterocyclic group mentioned for R^4 includes 3- through 13-membered, preferably 5- through 13-membered, heteroaromatic groups and non-aromatic saturated or unsaturated heterocyclic groups containing 1-4 hetero-atoms selected from among oxygen (O), sulfur (S) and nitrogen (N) as ring members.

The preferred heteroaromatic group includes mono-cyclic heteroaromatic groups such as furyl, thienyl, pyrrolyl, pyrrolinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, triazinyl, 1,2,3-triazolyl, triazolidinyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, etc., and fused heteroaromatic groups such as benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl,

benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthylidinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenathridinyl, phenanthrolinyl, indolidinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl, 1,2,4-triazolo[4,3-b]pyridazinyl, etc.

The preferred nonaromatic heterocyclic group includes oxiranyl, azetidinyl, oxetanyl, thietanyl, thiazolidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, tetrahydrofuryl, thioranyl, piperidyl, piperidinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl, oxazolino, hexamethyleneamino, etc.

As the heterocyclic group, a 5 to 7 membered heretocyclic group is prefereble, and a 5 to 6 membered heterocyclic group is more prefereble.

The above heterocyclic groups may each have 1 or more, preferably 1-3, suitable substituents, which can be the same as the above-mentioned substituents for hydrocarbon residue.

The spacer group mentioned for W includes C_{1-4} alkylene, e.g. methylene, ethylene, etc, C_{2-6} alkenylene, e.g. vinylene, butadienylene, etc, groups of the formula $-(CH_2)cNR^7-$, where c represents an integer of 0-3, R^7 represents hydrogen or C_{1-6} alkyl, e.g. methyl, ethyl, propyl, butyl, etc, -CO-, groups of the formula $-CONR^7-$, where R^7 is as defined above, -O-, -S(O)f-, where f represents an integer of 0 to 2, and -

$NR^7S(O)e$-, where e represents an integer of 0-2; R^7 is as defined above, among other groups.

The optionally substituted hydrocarbon residue of R^1 is preferably C_{1-20} hydrocarbon residue. Among others, C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{2-10} alkenyl, C_{6-14} aryl and C_{7-20} aralkyl are preferable.

As R^1, an optionally substitued C_{7-20} aralkyl is most preferable.

As preferable examples of the substituent in the optionally substituted hydrocarbon residue of R^1 is (1) halogen, (2) nitro, (3) cyano, (4) an optionally substituted hydroxyl group, (5) a group of the formula: $-S(O)f-R^6$ wherein f denotes an integer of 0 to 2, and R^6 is a hydrogen atom or an optionally substituted hydrocarbon residue, (6) an optionally substituted amino group or (7) an optionally substituted 5- or 6-membered heterocyclic group which contains 1 to 4 heteroatom(s) of oxygen, sulfur or nitrogen.

The group R^1 is preferably the group of the formula: $-(CH_2)_mQ$, wherein m is an integer of 0 to 3 and Q is an optionally substituted C_{6-14} aryl group, an optionally substituted C_{3-10} cycloalkyl group or an optionally substituted 5 to 13-membered heterocyclic group.

As the above optionally substituted C_{6-14} aryl group, a C_{6-14} aryl group which may have one to three substituent(s) of halogen, nitro, cyano, amino, carboxyl which may be optionally substituted, C_{1-6} alkylenedioxy, C_{1-6} alkoxy, C_{1-6} alkylthio or a group of the formula: $-A-R^{12}$, wherein A is a spacer group having the same meaning as W, and R^{12} is C_{1-6} alkyl. The optionally substituted carboxyl has the same meaning of the above group of the formula: $-CO-R^{11}$.

In particular, Q is preferably C_{6-14} aryl group optionally substituted by (1) halogen, (2) C_{1-6} alkoxy,

(3) C_{1-6} alkylthio, (4) a group of the formula: $-A-R^{12}$ (wherein A and R^{12} have the same meaning as defined above. Furthermore, Q is more preferably C_{6-14} aryl which may be substituted by (1) halogen, (2) C_{1-6} alkylthio or (3) C_{1-6} alkoxy. As the aryl, phenyl is most preferable.

As the preferable group of R^1, mention is made of a C_{7-20} aralkyl which is optionally substituted. As the preferable example of the substituent, mention is made of (1) halogen, (2) nitro, (3) hydroxy, (4) cyano, (5) C_{1-4} alkyl, (6) C_{1-4} alkylthio, (7) C_{1-4} alkoxy. Among others, (1) halogen and (2) C_{1-4} alkylthio is preferable, and C_{1-4} alkylthio is most preferable. As the C_{7-20} aralkyl, benzyl is most preferable.

As the optionally substituted amino group represented by R^8, mention is made of a group of the formula: $-NR^9R^{10}$, wherein R^9 and R^{10} are the same or different hydrogen, hydrocarbon residue, which has the same meaning as defined above, C_{1-6} acyl or heterocyclic group which is mentioned below.

As the preferred group of R^2, mention is made of those of R^1.

Further, as the group R^2, hydrogen or an optionally substituted C_{1-10} alkyl is preferable. As the alkyl, an optionally substituted C_{1-6} alkyl is more preferable, and furthermore an optionally substituted C_{1-4} alkyl is most preferable.

As the substituent on the alkyl of R^2, preferred examples are (1) halogen, (2) nitro, (3) cyano, (4) an optionally substituted hydroxyl group, (5) a group of the formula: $-S(O)f-R^6$, wherein f denotes an integer of 0 to 2, and R^6 is a hydrogen atom or an optionally substituted hydrocarbon residue, (6) an optionally substituted amino group or (7) an optionally

substituted 5- or 6-membered heterocyclic group which contains 1 to 4 heteroatoms of oxygen, sulfur or nitrogen. Among others, as substituents, (1) halogen, (2) nitro, (3) hydroxy, (4) cyano, (5) C_{1-4} alkylthio, (6) C_{1-4} alkoxy, (7) C_{1-6} alkyl-carbonyloxy, (8) C_{3-6} cycloalkyl-oxycarbonyloxy are preferred. In these groups, (1) C_{1-6} alkyl-carbonyloxy or (2) C_{3-6} cycloalkyl-oxycarbonyloxy is most preferable.

As the group R^3, preferable examples include (a) a C_{1-6} alkyl group which is substituted by (1) a C_{1-6} alkoxy-carbonyl group or (2) a group of the formula: $-NH-SO_2-R^{5'}$, wherein $R^{5'}$ is a C_{1-6} alkyl group or a C_{6-14} aryl group, (b) a C_{1-6} alkyl group which is substituted by a group of the formula: $-NH-SO_2-R^5$, wherein R^5 is (1) a C_{1-6} alkyl group which may optionally substituted by halogen or (2) or C_{6-14} aryl group, (c) a C_{1-6} alkyl group which is substituted by a group of the formula: $-NH-SO_2-R^{5'}$, wherein $R^{5'}$ is a C_{1-6} alkyl group or a C_{6-14} aryl group, (d) a C_{1-6} alkyl group which is substituted by a group of the formula: $-NH-SO_2-R^{5''}$, wherein $R^{5''}$ is a C_{1-3} alkyl group which may optionally be substituted by halogen or a phenyl group, (e) a C_{1-6} alkyl group which is substituted by a group of the formula: $-NH-SO_2-R^{5'''}$, wherein $R^{5'''}$ is a C_{1-3} alkyl group or a phenyl group, (f) a C_{1-6} alkyl group which is substituted by a group of the formula: $-NH-SO_2-R^{5''''}$, which $R^{5''''}$ is a C_{1-6} alkyl group, and (g) a C_{1-6} alkyl group which is substituted by a group of the formula: $-NH-SO_2\ -R^{5'''''}$, wherein $R^{5'''''}$ is a C_{1-3} alkyl group.

As the group R^4, an optionally substituted C_{6-14} aryl group, an optionally substituted C_{7-20} aralkyl group, an optionally substituted C_{3-7} cycloalkyl group, an optionally substituted carboxyl group of the formula $-CO-R^{11}$ as mentioned above or an optionally substituted

5- to 13-membered heterocyclic group which contains 1 to 4 heteroatoms of oxygen, sulfur or nitrogen (5- or 6-membered heterocyclic group is preferable), are preferable.

The substituent of the above groups are the same as those of hydrocarbon residue as mentioned above.

As preferred examples of the substituents, mention is made of (1) halogen, (2) nitro, (3) cyano, (4) C_{1-6} alkoxy which may optionally be substituted by C_{1-6} alkoxy, carboxyl, halogen, C_{1-6} alkyl-carbamoyl, 5 to 7 membered nitrogen-containing heterocyclic group, (5) C_{7-13} aralkyloxy, (6) C_{1-4} alkyl which may be substituted by hydroxy, oxo or C_{1-3} alkoxy, (7) C_{1-6} alkanoyl, (8) C_{1-4} alkylthio, (9) C_{2-6} alkenyloxy, (10) C_{1-6} alkoxy-carbonyl or (11) C_{1-6} alkyl-aminocarbonyl.

As the group R^4, preferred examples are a C_{6-14} aryl group, a C_{3-10} cycloalkyl group, a 5 to 13 membered heterocyclic group, or carboxyl group, each of these groups being optionally substituted, and an optionally substituted C_{6-14} aryl group is more preferable.

In the group R^4, as preferred examples of the substituents, mention is also made of C_{1-6} alkoxy which may optionally substituted by a C_{1-6} alkoxy, carboxyl, halogen, C_{1-6} alkyl-carbamoyl or 5 to 7 membered nitrogen-containing heterocyclic group. Additional preferred examples of R^4 are C_{6-14} aryl which may be substituted by (1) C_{1-6} alkoxy, which may be substituted by halogen or C_{1-6} alkoxy or (2) C_{1-6} alkylthio. A most preferred example of the group R^4 is C_{6-14} aryl which may optionally be substituted by an optionally substituted C_{1-6} alkoxy, especially C_{1-6} alkoxy which may optionally be substituted by C_{1-6} alkoxy.

Still other preferred examples of the group R^4 are phenyl which may be substituted by (1) C_{1-4} alkoxy which

may be substituted by C_{1-6} alkoxy, carboxy, C_{1-6} alkyl-carbamoyl, piperazinecarbonyl or halogen, (2) C_{7-8} aralkyloxy, (3) C_{1-4} alkyl which may optionally be substituted by hydroxy, oxo or C_{1-3} alkoxy, especially C_{1-4} alkyl which may optionally be substituted by C_{1-3} alkoxy, (4) C_{1-6} alkanoyl, (5) C_{2-4} alkenyloxy, (6) C_{1-6} alkoxy-carbonyl or (7) C_{1-6} alkyl-carbamoyl.

W is preferably a chemical bond or an spacer group of the formula -S(O)f-, wherein f represents an integer of 0-2, the formula -CO-, or the formula -CONR^7-, where R^7 represents C_{1-4} alkyl such as methyl, ethyl, propyl, butyl, etc. W is most preferably a chemical bond.

In the above definitions, C_{2-6} alkenyl is exemplified by vinyl, allyl, isopropenyl, butenyl, hexatrienyl, C_{2-4} alkenyl is exemplified by vinyl, allyl, isopropenyl, butenyl.

C_{6-14} aryl is exemplified by phenyl, naphthyl, anthryl, phenanthryl, acenaphthyl, anthracenyl, especially phenyl is most preferable.

C_{7-8} aralkyl is exemplified by benzyl and phenethyl.

C_{1-6} alkoxy is exemplified by methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, isobutoxy, s-butoxy, t-butoxy, pentyloxy, hexyloxy, C_{1-4} alkoxy is exemplified by methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, isobutoxy, s-butoxy, t-butoxy. C_{1-3} alkoxy is exemplified by methoxy, ethoxy, propoxy, isopropoxy.

Halogen is exemplified by fluorine, chlorine, bromine, iodine.

C_{1-6} alkyl is exemplified by methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, pentyl, hexyl. C_{1-4} alkyl is exemplified by methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl. C_{1-3} alkyl is exemplified by methyl, ethyl, n-propyl, isopropyl.

C_{3-10} cycloalkyl is exemplified by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl. C_{3-7} cycloalkyl is exemplified by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl. C_{3-6} cycloalkyl is exemplified by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl.

C_{1-6} acyl is exemplified by formyl and C_{1-6} alkanoyl of the formula: $-CO-R^{13}$, wherein R^{13} is methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, s-butyl, t-butyl, pentyl.

C_{2-6} alkanoyl is exemplified by the formula: $-CO-R^{13}$, wherein R^{13} has the same meaning as defined above. C_{1-4} acyl is exemplified by formyl and the formula: $-CO-R^{13'}$ (wherein $R^{13'}$ is methyl, ethyl, n-propyl, isopropyl.).

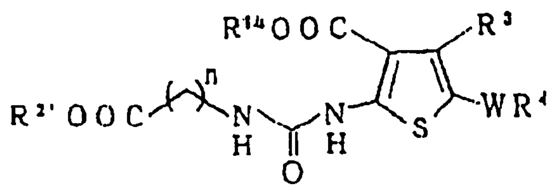
Preferable five to seven-membered heterocyclic groups which contain 1 to 4 heteroatoms of oxygen, sulfur or nitrogen are exemplified by thienyl, furyl, pyrrolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, triazolyl, tetrazolyl, furazanyl, tetrahydrofuryl, pyridyl, pyrimidinyl, pyridazynyl, oxadiazolyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, pyrrolinyl, pyrazolidinyl, pyrazolinyl, imidazolidinyl, imidazolinyl, imidazolyl, 1,2,3-triazinyl, 1,2,3-triazolidinyl, 1,2,3-triazolyl, 1,2,3,4-tetrazolyl, piperidinyl, piperazinyl, hexamethyleneaminyl, oxazolidinyl or thiazolidinyl. As more preferable heterocyclic groups, mention is made of 5 to 6 membered heterocyclic groups. In particular, pyrrolidinyl, pyrazolinyl, pyrazolyl, piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl are preferable.

In the above definition, the number of the substituent(s) is preferably 1 to 3.

The present compound (I) and their salts can be

produced by *per se* known methods. Typically, the present compound can be produced by the processes described below.

(a) The compound (I') in which R^1 is hydrogen and R^2 is an optionally substituted hydrocarbon residue, that is to say compound (IV') or a salt thereof can be produced by cyclizing a compound of the following general formula (II') or a salt thereof with a base.



(II')

wherein $R^{2'}$ represents an optionally substituted hydrocarbon residue; R^3, R^4, W and n are as defined hereinbefore; R^{14} represents hydrogen or an optionally substituted hydrocarbon residue being the same as above.

This reaction is carried out in a solvent that does not interfere with the reaction. The solvent that can be used includes but is not limited to alcohols such as methanol, ethanol, isopropyl alcohol, etc. and ethers such as dioxane, tetrahydrofuran, etc.

The base mentioned above may for example be an alkali metal alkoxide, e.g. sodium methoxide, sodium ethoxide, sodium isopropoxide, etc., or an alkali metal hydride, e.g. sodium hydride.

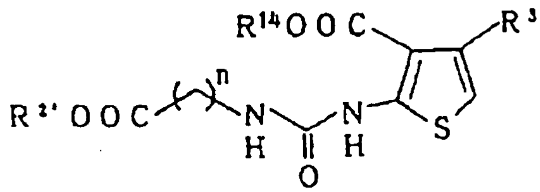
The amount of the base with respect to compound (II') is about 1.1-5 molar equivalents, preferably about 1.5-3 equivalents.

The reaction temperature may range from about 10°C to the boiling point of the solvent used and is preferably about 25°C to the boiling point of the solvent.

The reaction time is several minutes to a few days

and preferably about 10 minutes to 2 days.

(b) Compound (IV') or a salt thereof can be produced by cyclizing a compound of the following general formula (III) or a salt thereof in the presence of a base and subjecting the cyclization product to electrophilic substitution reaction for introducing a group of the formula $-WR^4$, where W and R^4 are as defined hereinbefore.



(III)

wherein $R^{2'}$ represents an optionally substituted hydrocarbon residue; R^3 is as defined hereinbefore; R^{14} represents hydrogen or an optionally substituted hydrocarbon residue; n represents a whole number of 1-3.

This cyclization reaction is conducted in a solvent that does not interfere with the reaction. The solvent that can be used includes but is not limited to alcohols such as methanol, ethanol, isopropyl alcohol, etc. and ethers such as dioxane, tetrahydrofuran, etc.

The base that can be used includes alkali metal alkoxides such as sodium methoxide, sodium ethoxide, sodium isopropoxide, etc. and alkali metal hydrides such as sodium hydride etc.

The proportion of the base with respect to compound (III) is about 1.1-5 molar equivalents and preferably about 1.5-3 equivalents.

The reaction temperature may range from about 10°C to the boiling point of the solvent used and is preferably about 25°C to the boiling point of the solvent.

The reaction time is several minutes to a few days and preferably about 10 minutes to 2 days.

This electrophilic substitution can be achieved by a per se known electrophilic substitution reaction. Specific examples of such reaction are the nitration reaction, e.g. the reaction using fuming nitric acid-concentrated sulfuric acid or sodium nitrate-concentrated sulfuric acid, acylation reaction, e.g. the reaction using an acid chloride-aluminum chloride, formylation reaction, e.g. the reaction using phosphorus oxychloride-N,N-dimethylformamide or N-methylformanilide, and halogenation reaction, e.g. the reaction using N-bromosuccinimide, bromine-pyridine, or sulfuryl chloride.

The electrophilic substitution reaction can be carried out under per se known reaction conditions. Typical sets of conditions are as follows. The nitration reaction is conducted in fuming nitric acid-concentrated sulfuric acid, sodium nitrate-concentrated sulfuric acid, or potassium nitrate-concentrated sulfuric acid at about 0-80°C. The acylation reaction is carried out using an alkanoyl chloride, e.g. acetyl chloride, propionyl chloride, etc, in a solvent that does not interfere with the reaction, e.g. nitrobenzene, nitromethane, carbon disulfide, etc, in the presence of a Lewis acid catalyst, e.g. aluminum chloride, titanium tetrachloride, etc, at about 0-100°C. The formylation reaction is carried out using phosphorus oxychloride-N,N-dimethylformamide/N-methylformanilide, oxalyl chloride-N,N-dimethylformamide/N-methylformanilide, thionyl chloride-N,N-dimethylformamide/N-methylformanilide in a solvent that does not interfere with the reaction, e.g. benzene, toluene, xylene, tetrahydrofuran, dioxane, 1,2-dichloroethane, etc, or in the absence of a solvent at about 15-130°C. The halogenation reaction is carried out using sulfuryl chloride, N-chlorosuccinimide, N-bromosuccinimide, bromine,

chlorine, or iodine in a solvent that does not interfere with the reaction, e.g. dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, pyridine, benzene, toluene, xylene, etc, at about 15-130°C.

The substituent group introduced by the above electrophilic substitution reaction can be subjected, where desired, to a functional group transformation reaction. This functional group transformation reaction can be carried out by the per se known transformation reaction. Specific examples of the reaction are reduction reaction, acylation reaction, sulfonylation reaction, alkylation reaction, diazo coupling reaction, Wittig reaction, halogenation reaction, halide-Grignard reaction, and coupling reaction with an organozinc reagent, an organoboron reagent or an organotin reagent.

(c) The compound (I') wherein R^1 represents an optionally substituted hydrocarbon residue and R^2 represents an optionally substituted hydrocarbon residue, that is to say compound (VI), or a salt thereof can be produced by reacting the compound (IV') or a salt thereof as prepared by the above procedure (a) or (b) with a compound of the general formula (V'): R^1-X (V'), wherein R^1 represents an optionally substituted hydrocarbon residue; X represents halogen, or a salt thereof.

The optionally substituted hydrocarbon residue mentioned for R^1 has the same meaning as defined hereinbefore. The halogen mentioned for X includes fluorine, chlorine, bromine, and iodine.

This reaction is conducted in a solvent that does not interfere with the reaction. The solvent that can be used includes ethers such as tetrahydrofuran, dioxane, etc., aromatic hydrocarbons such as benzene, toluene, xylene, etc., amides such as N,N-

dimethylformamide, N,N-dimethylacetamide, etc., dimethyl sulfoxide, and so on. This r action is preferably carried out under basic conditions, e.g. in the presence of potassium carbonate, sodium hydride, potassium hydride, potassium t-butoxide, or the like.

The proportion of compound (V') with respect to compound (IV') is about 1-5 molar equivalents and preferably about 1.1-2.5 equivalents.

When a base is used, its proportion is about 1-5 equivalents, preferably 1.1-3 equivalents, based on compound (IV').

The reaction temperature may range from about 10°C to the boiling point of the solvent used and is preferably about 20°C-130°C.

The reaction time ranges from several minutes to a few days and preferably from about 15 minutes to about 2 days.

(d) The hydroxyl group in the starting compound can be substituted by various kinds of groups. The reaction is carried out in an appropriate solvent, e.g. dimethylformamide (DMF), acetonitrile, acetone. To the solution of the starting compound is added halide such as alkyl halide, e.g. propyl iodide, isobutyl iodide, ethybromo acetate, or aralkyl halide, e.g. benzylchlolide. The mixture is stirred at 0 to 40°C for 2 to 18 hours.

For example, in the case of ethyl bromoacetate, the obtained acetic acid ester is hydrolyzed in an adequate solvent and base, e.g. iN NaOH solution in ethyl alcohol, at room temperature for 2 to 12 hours. The acetic acid compound is dissolved in an adequate solvent, e.g. tetrahydrofuran (THF). To the solution is added isobutyl chloroformate in the presence of an adequate base, e.g. Et_3N, and the reaction is carried out at 0°C for 1 to 4 hours. To the solution is added adequate amine derivatives, e.g. methylamine,

propylamine, piperidine. The reaction is carried out at 0°C to room temperature for 1 to 12 hours.

Said starting compound which has a hydroxyl group is produced by acid-hydrolysis of a compound such as one having an alkoxy group. The acid hydrolysis is carried out in a conventional manner such as by adding 1N hydrochloric acid in an appropriate solvent such as tetrahydrofuran or alcohol, e.g. methanol, ethanol, at 0°C to room temperature for one to 10 hours.

(e) The present compound (I'), wherein WR^4 is an alkanoyl- phenyl group can be produced by the introduction of a alkanoyl-phenyl group to the halogenated compound (WR^4=Br). The halogenated compound is obtained by the halogenation reaction with the starting compound (WR^4=H). The halogenation is carried out in an adequate solvent, e.g. carbontetrachloride or chloroform. To the solution is added N-bromosuccinimide and catalytic amount of 2,2'-azobis- (isobutyronitrile). The reaction is carried out at 100 to 120°C for 1 to 4 hours. The introduction reaction of alkanoyl phenyl group is carried out in an appropriate degased solvent, e.g. dimethoxyethane (DME). To the solution is added alkanoyl phenyl borate, palladium compound, e.g. $Pd(PPh_3)_4$(Ph=phenyl) and sodium carbonate (2M, Na_2CO_3). The alkanoyl phenyl borate is synthesized by the reaction of alkanoyl phenyl bromide with adequate borate, e.g. (i-$PrO)_3B$(Pro=propyl) in the presence of adequate base, e.g. BuLi (Bu=butyl). The introduction reaction is carried out at room temperature to 120°C for 1 to 12 hours under inert gas atmosphere.

(f) The present compound (I'), wherein WR^4 is alkylphenyl group can be produced by the similar manner as shown in (e) with alkyl phenyl borates instead of alkanoyl phenyl borates.

Any other group in the compound can be introduced

by any known *per se* known methods.

(g) The present compound (I), wherein R^3 is an alkoxycarbonyl group, can be produced by introducing a cyano group, and then subjecting the obtained compound to esterification.

In the reaction of the introduction of cyano group, the starting compound is dissolved in an appropriate solvent, e.g. dimethylsulfoxide (DMSO), and to the solution is added sodium cyanide. The reaction is carried out at 40 to 60°C for 2 to 12 hours.

The esterification reaction is carried out in an appropriate solvent such as ethyl alcohol. The reaction is conducted by mixing the starting compound and alcohol solution, e.g. ethyl alcohol, saturated with hydrochloric acid. The reaction is carried out at 80 to 120°C for 12 to 48 hours.

(h) The present compound (I'), wherein R^3 is an alkyl group which is substituted by a group $-NH-SO_2-R^5$, wherein R^5 is the same meaning as defined above, can be synthesized by (i) halogenation of this alkyl group and (ii) nucleophilic substitution of this halogen with a sulfonamide compound in the presence of appropriate base, e.g. sodium hydride.

The halogenation is carried out in an appropriate solvent, e.g. carbon tetrachloride. To the solution is added N-bromosuccinimide or catalytic amount of 2,2'-azobis(isobutyronitrile). The reaction is carried out at 100 to 120°C for 1 to 4 hours.

The nucleophilic substitution reaction is carried out in a similar manner as described in the above process (P) on the reaction of the compound (IV') and (V'). Particularly, in an appropriate solvent such as N,N-dimethylformamide (DMF). To the solution is added sodium hydride washed with n-hexane and sulfonamide derivatives, e.g. methanesulfonamide, ethanesulfonamide, benzenesulfonamide. The reaction is

carried out at 0 to 40°C for 1 to 24 hours.

(i) The compound (I') wherein R^2 is hydrogen, that is to say compound (VII) or (VII'), or a salt thereof, can be obtained by subjecting the compound (IV') or (VI), or a salt thereof, as produced in the above manner to a reaction for conversion of R^2 to hydrogen.

The reaction for converting R^2 to hydrogen or from esters to carboxylic groups may for example be a alkali-hydrolysis reaction. This hydrolysis reaction is conducted by reacting compound (IV') or (VI), or a salt thereof, with a base in a solvent that does not interfere with the reaction. The solvent that can be used for this reaction includes alcohols such as methanol, ethanol, isopropyl alcohol, etc., ethers such as tetrahydrofuran, dioxane, etc., amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc., and dimethyl sulfoxide, among others. The base that can be used includes alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide, etc., alkaline earth metal hydroxides such as calcium hydroxide, barium hydroxide, etc., and alkali metal carbonates such as potassium carbonate, sodium carbonate, etc. The proportion of the base to compound (IV') or (VI) is about 1-10 molar equivalents and preferably about 1.5-5 equivalents. The reaction temperature may range from about 10°C to the boiling point of the solvent used and is preferably about 15°-100°C. The reaction time is several minutes to a few days and preferably about 15 minutes to two days.

The compound of the item (28) aforementioned can be produced by subjecting a starting compound (I') in which R^3 is alkoxycarbonyl-methyl to an alkali-hydrolysis as mentioned above.

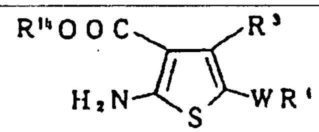
(j) The present compound (I'), wherein R^2 is the optionally substituted hydrocarbon residue such as pivaloyloxymethyl or 1-(cyclohexyloxycarbonyloxy)ethyl

can be synthesized by the condensation reaction of the compound (I′,R^2=H) with chloride agents (e.g. pivaloyloxymethyl chloride, 1-(cyclohexyloxycarbonyloxy)ethyl-1-chloride) or acid anhydride agents, e.g. pivalic anhydride, in an appropriate solvent, e.g. dimethylformamide (DMF), in the presence of adequate base (e.g. K_2CO_3) and potassium iodide (KI). The reaction is carried out at 0°C to room temperature for 2 to 24 hours.

The starting compounds (II′) and (III), as well as salts thereof, which are to be employed in the above production processes can be produced typically by the following alternative processes A and B.

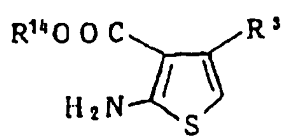
1. Process A

In this process, either a compound of the general formula (VIII) or a salt thereof or a compound of the general formula (VIII′) or a salt thereof is reacted with an isocyanic acid ester derivative.



(VIII)

wherein R^3, R^4, R^{14}, W, and n are as defined hereinbefore,



(VIII′)

wherein R^3 and R^{14} are as defined as hereinbefore.

The isocyanic acid derivative mentioned above may for example be an isocyanate derivative of the formula $R^{14}OOC-(CH_2)_n-NCO$, wherein R^{14} and n are as defined hereinbefore.

The reaction of compound (VIII) or compound (VIII′), or a salt thereof, with said isocyanate derivative is carried out in a solvent which does not interfere with the reaction, e.g. tetrahydrofuran,

pyridine, dioxane, benzene, dichloromethane, 1,2-dichloroethane, toluene, xylene, etc, at about 15-130°C and preferably at about 25-130°C.

The isocyanate derivative is used in a proportion of about 1-5, preferably about 1.1-2.5 molar equivalents, relative to compound (VIII) or (VIII').

The reaction time is several minutes to a few days and preferably about 15 minutes to about 2 days.

2. Process B

This process comprises reacting compound (VIII) or (VIII'), or a salt thereof, with phosgene or the equivalent, e.g. triphosgene of bis(trichloromethyl) carbonate or the like, diphosgene of trichloromethyl chloroformate or the like, etc, to give the isocyanate derivative and adding an amine, e.g. a compound of the formula $R^{14}OOC-(CH_2)n-NH_2$, where R^{14} and n are as defined hereinbefore.

The reaction between compound (VIII) or (VIII'), or a salt thereof, and phosgene or the equivalent is conducted in a solvent that does not interfere with the reaction, e.g. dioxane, tetrahydrofuran, benzene, toluene, xylene, 1,2-dichloroethane, chloroform, etc, at about 15-130°C and preferably at about 25-130°C.

Phosgene or the equivalent thereof is used in a proportion of about 0.5-2 molar equivalents, preferably about 0.9-1.1 equivalents, with respect to compound (VIII) or (VIII').

The reaction time is several minutes to a few days and preferably about 15 minutes to about two days.

The amine addition reaction is carried out in a solvent that does not interfere with the reaction, e.g. pyridine, tetrahydrofuran, dioxane, benzene, dichloromethane, 1,2-dichloroethane, toluene, xylene, etc, at about 15-130°C and preferably at about 25-130°C.

The amine is used in a proportion of about 1-5 molar equivalents, preferably about 1.1-3 equivalents,

with respect to compound (VIII) or (VIII').

The reaction time is several minutes to a few days and preferably about 15 minutes to about two days.

The compound (VIII) or a salt thereof for use in the above reaction can be produced by the following process.

A ketone having an active methylene group, e.g. a compound (IX) of the formula R^3-CO-CH_2-WR^4, where R^3, R^4 and W are as defined hereinbefore, is reacted with a cyanoacetic ester derivative and sulfur according to the method of K. Gewald, E. Schinke and H. Bettcher, Chem. Ber., 99, 94-100, 1966, to give compound (VIII) or a salt thereof. Thus, the above-mentioned ketone and the cyanoacetate derivative are heated together under reflux in a solvent that does not interfere with the reaction, e.g. benzene, toluene, etc, in the presence of acetic acid and ammonium acetate to give the alkylidenecyanoacetate derivative which is then heated in a solvent that does not interfere with the reaction, e.g. methanol, ethanol, etc, in the presence of sulfur and a base, e.g. an organic base such as triethylamine, ethyldiisopropylamine, dimethylaminopyridine, etc, at a temperature of about 50-80°C to give 2-aminothiophene derivative i.e. Compound (VIII).

Compound (VIII') can be synthesized by the method of K. Gewald (Chem. Ber., 98, 3571-3577 (1965) (K. Gewald) and Chem. Ber., 99, 2712-2715 (1966) (K. Gewald and E. Schinke).

In this specification, "the present compound" means the compounds of this invention, such as the compound (I), the compound (I') and the compound of the above item (28).

The salt of the present compound thus obtained is preferably a physiologically acceptable acid addition salt. Such addition salt may for example be any of

salts with inorganic acids, e.g. hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc, and salts with organic acids, e.g. formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, etc. Where the present compound of the invention has an acidic group such as -COOH, the present compound may form salts with inorganic bases, e.g. alkali metals or alkaline earth metals such as sodium, potassium, calcium, magnesium, etc, or ammonia, or organic bases, e.g. trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N'-dibenzylethylenediamine, etc.

The compound or salt of the invention as produced by the above-described technology can be isolated and purified by the conventional procedures such as recrystallization, distillation, and chromatography, among other fractionation techniques. Where the present compound is obtained as a free compound, it can be converted to a salt by a per se known method or any method analogous therewith. Conversely where a salt is obtained, it can be converted to the free compound or a different salt by a per se known method or any method analogous therewith.

The salts of the compounds (II) to (IX) can also be salts similar to the salts of compound (I).

Where the present compound or salt of the invention is an optically active compound, it can be fractionated into the d- and ℓ-compounds by a conventional optical resolution technique.

The present compound has only a low toxic potential and can, therefore, be safely used.

The endothelin antagonist composition of the present invention has remarkably potent endothelin

receptor antagonist activity and can be administered as an endothelin antagonist to mammals, e.g. rat, mouse, rabbit, cat, dog, bovine, equine, and human being. Specifically, it can be used safely as a therapeutic drug for acute renal failure, myocardial infarction, liver disorder, angina pectoris, cerebral infarction, cerebrovasospasm, hypertension, kidney disease, asthma, ectopic angina, Raynaud's syndrome, pulmonary hypertension, surgical shock, chronic cardiac insufficiency, atherosclerosis, cardiac hypertrophy and migraine, among other diseases, as a prophylactic or therapeutic drug for organ, e.g. liver, surgery- or transplant-associated organic hypofunction, or as a prophylactic agent for post-PTCA vascular restenosis. Particularly, the composition is of great use as a therapeutic drug for acute renal failure, myocardial infarction, hepatic disorder, hypertension, and pulmonary hypertension, as a prophylactic or therapeutic drug for organ, e.g. liver, surgery- or transplant-associated organic hypofunction, or as a prophylactic drug for post-PTCA vascular restenosis. Furthermore, the compound of the present invention can be used as an inhibitor for vasoconstriction, such as an inhibitor for vasoconstriction of coronary artery, coronary vein, cerebrovascular system or pulmonary vascular system.

When the present compound or a salt thereof is to be administered to a human being, the compound as such or in the form of a pharmaceutical composition formulated with a suitable pharmacologically acceptable carrier, excipient or diluent can be safely administered orally or non-orally.

The pharmaceutical composition mentioned above may be provided in various dosage forms such as oral dosage forms, e.g. powders, granules, capsules, tablets, etc., injections, drip injections, dosage forms for external

application, e.g. nasal dosage forms and transdermal drug delivery systems, and suppositories, e.g. rectal suppositories, vaginal suppositories.

These dosage forms can be manufactured by the established pharmaceutical procedures.

The present compound or salt of the invention can be formulated with a dispersant, e.g. Tween 80, Atlas Powder Co., U.S.A., HOC 60, Nikko Chemicals Co., polyethylene glycol, carboxymethylcellulose, sodium alginate, etc., a preservative, e.g methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, benzyl alcohol, etc., an isotonizing agent, e.g. sodium chloride, mannitol, sorbitol, glucose, etc., and other additives to provide an aqueous injection, or dissolved, suspended or emulsified in vegetable oil, e.g. olive oil, sesame oil, cottonseed oil, corn oil, etc., propylene glycol, or the like to provide an oily injection.

For the manufacture of oral dosage forms, the present compound or salt of the invention is formulated with, for example, an excipient, e.g. lactose, sucrose, starch, etc., a disintegrator, e.g. starch, calcium carbonate, etc., a binder, e.g. starch, gum arabic, carboxymethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose, etc., and/or a lubricant, e.g. talc, magnesium stearate, polyethylene glycol 6000, etc., and compressed in the per se conventional manner. Where necessary, for masking the taste or insuring enteric or sustained release, the compressed composition can be coated by the per se known technique to provide an oral dosage form. The coating agent that can be used includes but is not limited to hydroxypropylmethylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, polyoxyethylene glycol, Tween 80, Pluronic F68, cellulose acetate phthalate,

hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, Eudragit, Rohm & Haas Co., Germany; methacrylic-acrylic acid copolymer, and pigments, e.g. red iron oxide, titanium dioxide, etc.. In the manufacture of an enteric release dosage form, it is preferable to provide an intermediate phase between an enteric phase and a drug-containing phase for phase-to-phase isolation.

For the manufacture of dosage forms for external application, the present compound or salt of the invention can be processed into solid, semisolid or liquid preparations. To provide a solid preparation, for instance, the present compound or a salt thereof is used as it is or in the form of a powdery composition formulated with an excipient, e.g. glycol, mannitol, starch, microcrystalline cellulose, etc., a thickener, e.g. natural gums, cellulose derivatives, acrylic polymers, etc., and other additives. A liquid preparation can be substantially similar to the injection mentioned above and may be an oily or aqueous suspension. The semisolid preparation can be an aqueous or oleaginous gel or ointment. To any of these preparations, a pH control agent, e.g. carbonic acid, phosphoric acid, citric acid, hydrochloric acid, sodium hydroxide, etc. and an antiseptic, e.g. p-hydroxybenzoic esters, chlorobutanol, benzalkonium chloride, etc. can be added.

For the production of suppositories, the present compound or salt of the invention can be processed into oleaginous or hydrous solid, semisolid or liquid suppositories in accordance with per se known production procedures. The oleaginous base that can be used for the above composition includes higher fatty acid glycerides, e.g. caccao butter, witepsols, Dynamite Nobel, Germany, medium fatty acid glycerides, e.g. miglyols, Dynamite Nobel, Germany, etc., and

vegetable oils, e.g. sesame oil, soybean oil, cottonseed oil, etc.. The water-soluble base includes polyethylene glycols, propylene glycol, and the hydrogel base that can be used includes natural gums, cellulose derivatives, vinyl polymers, acrylic polymers, and so on.

The daily dosage of the present compound varies with the severity of illness, the recipient's age, sex, body weight, and sensitivity, administration time and interval, the property, recipe, and type of dosage form, and species of active ingredient, among other variables, and cannot be stated in general terms. Usually, however, the recommended dosage is about 0.01-10 mg, preferably about 0.03-3 mg, per kilogram body weight of the mammal and the above amount is usually administered once or in up to 4 divided doses a day.

The compound of the present invention has particularly high endothelin receptor antagonist activity. Moreover, the compound is highly amenable to oral administration and features a sustained action.

The following examples are intended to describe the present invention in further detail and should by no means be construed as defining the scope of the invention.

The ^{1}H-NMR spectra shown were determined with a Varian Gemini 200 (200 MHz) spectrometer or Bruker AM-500 (500 MHz) spectrometer using tetramethylsilane as internal standard and all δ values were expressed in ppm.

The symbols used have the following meanings.

s: singlet, d: doublet, t: triplet, q: quartet, dt: double triplet, m: multiplet, br: broad, J: coupling constant.

Reference Example 1

Production of ethyl 2-amino-4-methyl-5-(4-methoxyphenyl)thiophene-3-carboxylate:

A mixture of 4-methoxyphenylacetone (16.5 g, 0.10 mol), ethyl cyanoacetate (12.2 g, 0.10 mol), ammonium acetate (1.55 g, 20 mmol), acetic acid (4.6 ml, 80 mmol), and benzene (20 ml) was refluxed for 24 hours, with the byproduct water being removed with a Dean-Stark trap. After cooling, the reaction mixture was concentrated under reduced pressure and the residue was distributed between dichloromethane and sodium hydrogen carbonate-water. The organic layer was washed with NaCl-water and dried ($MgSO_4$) and the solvent was distilled off under reduced pressure. The residue was dissolved in ethanol (30 ml), and sulfur (3.21 g, 0.10 mol) and diethylamine (10.4 ml, 0.10 mol) were added. This mixture was stirred at 50-60°C for 2 hours and then concentrated and the residue was extracted with ethyl acetate. The extract was washed with NaCl-water and dried ($MgSO_4$) and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography and crystallized from ether-hexane to provide light-yellow platelets (11.5 g, 40%). m.p. 79-80°C.

Elemental analysis for $C_{15}H_{17}NO_3S$

	C (%)	H (%)	N (%)	S (%)
Calcd.:	61.83;	5.88;	4.81;	11.01
Found :	61.81;	5.75;	4.74;	10.82

^1H-NMR (200 MHz, $CDCl_3$) δ: 1.37 (3H, t, J=7.1 Hz), 2.28 (3H, s), 3.83 (3H, s), 4.31 (2H, q, J=7.1 Hz), 6.05 (2H, br s), 6.91 (2H, d, J=8.8 Hz), 7.27 (2H, d, J=8.8 Hz).

IR (KBr): 3426, 3328, 1651, 1586, 1550, 1505, 1485 cm^{-1}.

FAB-MS m/z: 291 (M^+).

Reference Example 2

(1) Production of ethyl 2,4(1H,3H)-dioxo-6-(4-methoxyphenyl)thieno[2,3-d]pyrimidine-3-acetate:

To a pyridine solution (30 ml) of the ethyl 2-

amino-4-methyl-5-(4-methoxyphenyl)thiophene-3-carboxylate obtained in Reference Example 1 (8.00 g, 27.0 mmol) was added ethyl isocyanatoacetate (4.54 ml, 40.5 mmol) dropwise and the mixture was stirred at 50°C for 2 hours. This reaction mixture was concentrated to dryness and the residue was distributed between ethyl acetate and ammonium chloride-water. The aqueous layer was extracted with ethyl acetate. The extracts were combined, washed with NaCl-water, and dried ($MgSO_4$) and the solvent was distilled off under reduced pressure. The residue was suspended in ethanol (100 ml) and following addition of potassium tert-butoxide (6.06 g, 54.0 mmol), the suspension was stirred at room temperature for 3 hours. To this reaction mixture was added 1N-HCl (50 ml) with ice-cooling and the ethanol was distilled off under reduced pressure. The resulting crystals were collected by filtration, rinsed with water-ethanol, and dried in vacuo over phosphorus pentoxide to provide white powders (11.0 g, 96%). For use as a sample for elemental analysis, the above powders were recrystallized from ethanol to provide colorless crystals. m.p. 164-165°C.

(2) Using ethyl 2-amino-4-methylthiophene-3-carboxylate, the procedure of Reference Example 2 (1) was repeated to provide ethyl 2,4(1H,3H)-dioxo-5-methylthieno[2,3-d]pyrimidine-3-acetate. Yield 94%, amorphous.

(3) To a solution of ethyl 2,4(1H,3H)-dioxo-5-methylthieno[2.3-d]pyrimidine-3-acetate obtained in the above item (2) in chloroform was added N-bromosuccinimide. Then the mixture was refluxed for 2 hours to provide ethyl 2,4(1H,3H)-dioxo-5-methyl-6-bromothieno[2,3-d]pyrimidine-3-acetate. Yield 86%, amorphous.

<u>Reference Example 3</u>

Production of ethyl 2,4(1H,3H)-dioxo-6-(4-hydroxy-

phenyl)-5-methylthieno[2,3-d]pyrimidine-3-acetate:

To an ice-cooled mixture of aluminum chloride (2.90 g, 21.7 mmol), methyl disulfide (2.45 ml, 27.2 mmol), and dichloromethane (60 ml) was added a solution of the compound obtained in Reference Example 2 (2.0 g, 5.34 mmol) in dichloromethane (40 ml) dropwise and the mixture was stirred at room temperature for 20 hours. The reaction mixture was then poured in ice-water and the dichloromethane was distilled off under reduced pressure. This suspension was extracted with ethyl acetate and the extract was washed with NaCl-water and dried ($MgSO_4$). The solvent was then distilled off under reduced pressure and the residue was purified by silica gel column chromatography to provide white powders (1.64 g, 85%). For use as a sample for elemental analysis, the powders were recrystallized from ethyl acetate to provide colorless crystals. m.p. 240-242°C.

Elemental analysis for $C_{17}H_{16}N_2O_5S \cdot 0.1H_2O$

	C (%)	H (%)	N (%)
Calcd.:	56.38;	4.51;	7.73
Found :	56.28;	4.48;	7.64

^{1}H-NMR (200 MHz, DMSO-d_6) δ: 1.22 (3H, t, J=7.1 Hz), 2.37 (3H, s), 4.15 (2H, q, J=7.1 Hz), 4.59 (2H, s), 6.85 (2H, d, J=8.6 Hz), 7.26 (2H, d, J=8.6 Hz), 9.73 (1H, s), 12.39 (1H, s).

IR (KBr): 3356, 2992, 1720, 1690, 1667, 1611, 1593, 1568, 1537, 1502 cm^{-1}.

Reference Example 4

Production of ethyl 2,4(1H,3H)-dioxo-6-(4-hydroxyphenyl)-1-(2-methylthiobenzyl)-5-methylthieno[2,3-d]-pyrimidine-3-acetate:

To a solution of the compound obtained in Reference Example 3 (0.60 g, 1.66 mmol) in pyridine (8 ml) was added acetic anhydride (3 ml, 31.8 mmol) and the mixture was stirred at room temperature for 3

hours. This reaction mixture was concentrated and the residue was distributed between ethyl acetate and diluted hydrochloric acid. The aqueous layer was extracted with ethyl acetate. The organic layers were combined, washed with NaCl-water, and dried ($MgSO_4$) and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography to provide a white amorphous solid (0.57 g). To a solution of this amorphous solid in dimethylformamide (5 ml) were added potassium carbonate (0.38 g, 2.75 mmol) and 2-methylthiobenzyl chloride (0.65 g, 4.15 mmol) and the mixture was stirred at room temperature for 22 hours. This reaction mixture was concentrated and the residue was distributed between ethyl acetate and NaCl-water. The aqueous layer was extracted with ethyl acetate. The organic layers were combined, washed with NaCl-water, and dried ($MgSO_4$) and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography to provide a white amorphous solid (0.60 g). This amorphous solid was dissolved in methanol (18 ml)-tetrahydrofuran (12 ml) and a solution of potassium carbonate (0.313 g, 2.26 mmol) in water (8 ml) was added dropwise. The mixture was stirred at room temperature for 30 minutes and after 1N-hydrochloric acid (5 ml) was added under ice-cooling, the mixture was extracted with ethyl acetate. The extract was washed with NaCl-water and dried ($MgSO_4$), and the solvent was distilled off under reduced pressure. The residue was crystallized from ether to provide colorless crystals (4.33 g, 78%). m.p. 177-178°C.

Elemental analysis for $C_{25}H_{24}N_2O_5S_2 \cdot 1/10H_2O$

	C (%)	H (%)	N (%)
Calcd.:	60.25;	4.89;	5.62
Found :	60.09;	4.66;	5.57

^1H-NMR (200 MHz, $CDCl_3$) δ: 1.32 (3H, t, J=7.2 Hz), 2.45

(3H, s), 2.52 (3H, s), 4.28 (2H, q, J=7.2 Hz), 4.87 (2H, s), 5.28 (2H, s), 5.75 (1H, s), 6.78 (2H, d, J=8.6 Hz), 6.97-7.14 (4H, m), 7.21-7.34 (2H, m).

IR (KBr): 3346, 2978, 1752, 1700, 1651, 1613, 1591, 1564, 1535, 1481 cm^{-1}.

Reference Example 5

(1) Using the compound obtained in Reference Example 3, the procedure of Reference Example 4 was repeated except that 2-chloro-6-fluorobenzyl chloride was used in lieu of 2-methylthiobenzyl chloride to provide ethyl 2,4(1H,3H)-dioxo-6-(4-hydroxyphenyl)-1-(2-chloro-6-fluorobenzyl)-5-methylthieno[2,3-d]pyrimidine-3-acetate. Yield 59%, amorphous.

(2) Using the compound obtained in Reference Example 2 (3), the procedure of Reference Example 4 was repeated to provide ethyl 2,4(1H,3H)-dioxo-1-(2-methylthiobenzyl)-5-methylthieno[2,3-d]pyrimidine-3-acetate. Yield 87%, amorphous.

Reference Example 6

Production of ethyl 2,4(1H,3H)-dioxo-6-(4-methoxymethoxyphenyl)-1-(2-methylthiobenzyl)-5-methylthieno[2,3-d]pyrimidine-3-acetate:

To a suspension of sodium hydride (60% in oil, 500 mg, 12.5 mmol) in dimethylformamide (20 ml) was added a solution of the compound obtained in Reference Example 4 (2.0 g, 3.7 mmol) in dimethylformamide (30 ml) dropwise in a nitrogen gas stream under ice-cooling. The mixture was stirred at the same temperature for 30 minutes and, then, chloromethyl methyl ether (1.0 g, 12.4 mmol) was added dropwise. This mixture was stirred at room temperature for 16 hours and then concentrated, and the residue was distributed between ethyl acetate and aqueous ammonium chloride solution. The aqueous layer was extracted with ethyl acetate. The extracts were combined, washed with NaCl-water, and

dried ($MgSO_4$) and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography and recrystallized from ethyl acetate-hexane to provide colorless crystals (1.05 g, 59%). m.p. 133-134°C.

Elemental analysis for $C_{27}H_{28}N_2O_6S$

	C (%)	H (%)	N (%)
Calcd.:	63.76;	5.55;	5.51
Found :	63.48;	5.62;	5.37

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.30 (3H, t, J=7.1 Hz), 1.43 (3H, t, J=7.0 Hz), 2.49 (3H, s), 3.87 (3H, s), 4.05 (2H, q, J=7.0 Hz), 4.25 (2H, q, J=7.1 Hz), 4.83 (2H, s), 5.24 (2H, s), 6.86-6.94 (4H, m), 7.09-7.14 (1H, m), 7.22-7.31 (3H, m).

IR (KBr): 2984, 1758, 1707, 1665, 1607, 1562, 1535, 1477 cm^{-1}.

Reference Example 7

The compound obtained in Reference Example 5 was reacted with 2-chloro-6-fluorobenzyl chloride in lieu of chloromethyl methyl ether to provide ethyl 2,4(1H,3H)-dioxo-6-(4-isobutoxyphenyl)-1-(2-chloro-6-fluorobenzyl)-5-methylthieno[2,3-d]pyrimidine-3-acetate. Yield 29%, amorphous.

Reference Example 8

Production of ethyl 2,4(1H,3H)-dioxo-5-bromomethyl-1-(2-methylthiobenzyl)-6-(4-methoxymethoxyphenyl)thieno[2,3-d]pyrimidine-3-acetate:

A mixture of the compound obtained in Reference Example 6 (1.20 g, 2.22 mmol), N-bromosuccinimide (0.4 g, 2.25 mmol), α,α'-azobisisobutyronitrile (50 mg), and carbon tetrachloride (50 ml) was refluxed for 4 hours. After cooling, the insolubles were filtered off and the filtrate was diluted with dichloromethane. The organic layer was washed with NaCl-water and dried ($MgSO_4$) and the solvent was distilled off under reduced pressure to provide a yellow amorphous solid (2.0 g).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.28 (3H, t, J=7.2 Hz), 2.53 (3H, s), 3.50 (3H, s), 4.26 (2H, q, J=7.2 Hz), 4.80 (2H, s), 4.89 (2H, s), 5.22 (2H, s), 5.36 (2H, s), 7.00-7.50 (8H, m).

Reference Example 9

Production of ethyl 2,4(1H,3H)-dioxo-6-(4-methoxyphenyl)-1-(2-methylthiobenzyl)-5-methylthieno[2,3-d]-pyrimidine-3-acetate:

To a solution of the compound obtained in Reference Example 2 (2.0 g, 5.35 mmol) in dimethylformamide (25 ml) were added potassium carbonate (1.1 g, 7.98 mmol), potassium iodide (catalyst amount), and 2-methylthiobenzyl chloride (1.2 g, 6.96 mmol) and the mixture was stirred at room temperature for 18 hours. This reaction mixture was concentrated and the residue was distributed between ethyl acetate and NaCl-water. The aqueous layer was extracted with ethyl acetate. The organic layers were combined, washed with NaCl-water, and dried ($MgSO_4$) and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography to provide a light-yellow amorphous solid (1.8 g, 66%). Recrystallization from ether gave colorless crystals. m.p. 144-145°C.

Reference Example 10

Starting with the compound obtained in Reference Example 2, the procedure of Reference Example 9 was otherwise repeated to provide ethyl 2,4(1H,3H)-dioxo-6-(4-methoxyphenyl)-1-(2-chloro-6-fluorobenzyl)-5-methylthieno[2,3-d]pyrimidine-3-acetate. Yield 95%, amorphous.

Reference Example 11

Starting with the compounds obtained in Reference Examples 9 and 10, respectively, the procedure of Reference Example 8 was repeated to provide the following compounds.

Compound 1: Ethyl 2,4(1H,3H)-dioxo-6-(4-methoxyphenyl)-1-(2-methylthiobenzyl)-5-bromomethylthieno[2,3-d]pyrimidine-3-acetate. Yield 95%, amorphous.
Compound 2: Ethyl 2,4(1H,3H)-dioxo-6-(4-methoxyphenyl)-1-(2-chloro-6-fluorobenzyl)-5-bromomethylthieno[2,3-d]pyrimidine-3-acetate. Yield 100%, amorphous.
Compound 3: Ethyl 2,4(1H,3H)-dioxo-6-(4-isobutoxyphenyl)-1-(2-chloro-6-fluorobenzyl)-5-bromomethylthieno[2,3-d]pyrimidine-3-acetate. Yield 60%, amorphous.

Reference Example 12

In accordance with the similar manner of Reference Examples 6 and 8 the following compounds were obtained.

Compound 1: Ethyl 2,4(1H,3H)-dioxo-5-bromomethyl-1-(2-methylthiobenzyl)-6-(4-propoxyphenyl)thieno[2,3-d]pyrimidine-3-acetate. amorphous.

Reference Example 13

Production of ethyl {2,4(1H,3H)-dioxo-5-methyl-1-(2-methylthiobenzyl)-6-(4-(2-methoxyethyl)phenyl)-thieno[2,3-d]pyrimidine-3-acetate:

To a mixture of ethyl {2,4(1H,3H)-dioxo-6-bromo-5-methyl-1-(2-methylthiobenzyl)thieno[2,3-d]pyrimidine-3-acetate (1.0 g, 2.07 mmol) obtained in Reference Example 5(2), 4-(methoxyethylphenyl)boronic acid (1.0 g, 5.56 mmol), and 2M sodium carbonate (5.2 ml, 10.4 mmol) in 1,2-dimethoxyethane (50 ml) was added $Pd(PPh_3)_4$(Ph denotes phenyl) (358 mg, 0.31 mmol) under argon atmosphere. The mixture was stirred under reflux for 5 hour and filtered through celite. The filterate was partitioned between ethyl acetate and brine. The aqueous phase was separated and extracted with ethyl acetate. The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel with ethyl acetate and n-hexane (1:5 - 1:3) to give the product (860 mg, 77%) as colorless amorphous solid.

Recrystallization from ethyl acetate and nhexane gave product (594 mg) as colorless powder, m.p. 126-128°C.

Reference Example 14

Production of ethyl 2,4(1H,3H)-dioxo-5-bromomethyl-1-(2-methylthiobenzyl)-6-(4-(2-methoxyethyl)phenyl)thieno[2,3-d]pyrimidine-3-acetate:

A mixture of ethyl 2,4(1H,3H)-dioxo-5-methyl-1-(2-methylthiobenzyl)-6-(4-(2-methoxyethyl)phenyl)thieno [2,3-d]pyrimidine-3-acetate (600 mg, 1.11 mmol) obtained in Reference Example 13, N-bromosuccinimide (198 mg, 1.11 mmol) and 2,2'-azobisisobutyronitrile (18 mg, 0.11 mmol) in chloroform (30 ml) was stirred under reflux for 1.5 hour. The mixture was partitioned between CH_2Cl_2+brine. The organic layer was separated and washed with brine, dried over $MgSO_4$ and concentrated in vacuo to afford a pale yellow amorphous (730 mg, 44% purity).

Reference Example 15

Production of ethyl 2,4(1H,3H)-dioxo-6-(4-methoxyphenyl)-1-(2-methylthiobenzyl)-5-(cyanomethyl)thieno[2,3-d]pyrimidine-3-acetate:

In dimethyl sulfoxide (DMSO) (3 ml) was dissolved the compound obtained in Reference Example 11 (1) (0.67 g, 1.0 mmol) followed by addition of sodium cyanide (50 mg, 1.0 mmol) and the mixture was stirred at 60°C for 6 hours. After cooling, this reaction mixture was poured in iced water (100 ml) and extracted with ethyl acetate (50 ml) and methylene chloride (100 ml, twice). The extracts were pooled, washed with NaCl-water, and dried ($MgSO_4$) and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography to provide a light-yellow amorphous solid (0.20 g, 38%).

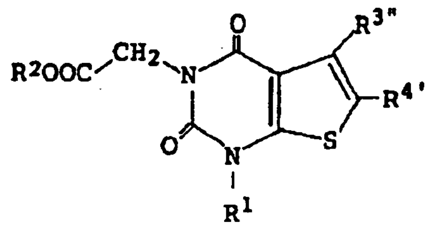
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.33 (3H, t, J=7.1 Hz), 2.52 (3H, s), 3.82 (3H, s), 3.94 (2H, s), 4.25 (2H, q, J=7.1 Hz), 4.88 (2H, s), 5.38 (2H, s), 6.95 (2H,

d), 7.05 (1H, d), 7.17 (1H, t), 7.34 (2H, d), 7.20-7.40 (2H, m).

IR (KBr): 2978, 2254, 1676, 1607, 1568, 1539, 1483, 1257 cm^{-1}.

The compounds shown in the above Reference Examples are listed in the Table 1.

Table 1



Reference Example No.	R^1	R^2	$R^{3''}$	$R^{4'}$
2(1)	H	ethyl	H	methoxyphenyl
2(2)	H	ethyl	methyl	H
2(3)	H	ethyl	methyl	bromo
3	H	ethyl	methyl	4-hydroxyphenyl
4	2-methylthio-benzyl	ethyl	methyl	4-hydroxyphenyl
5(1)	2-chloro-6-fluorobenzyl	ethyl	methyl	4-hydroxyphenyl
5(2)	2-methylthio-benzyl	ethyl	methyl	bromo
6	2-methylthio-benzyl	ethyl	methyl	4-methoxy-methoxyphenyl
7	2-chloro-6-fluorobenzyl	ethyl	methyl	4-isobutoxyphenyl
8	2-methylthio-benzyl	ethyl	bromomethyl	4-methoxy-methoxyphenyl
9	2-methylthio-benzyl	ethyl	methyl	4-methoxyphenyl
10	2-chloro-6-fluorobenzyl	ethyl	methyl	4-methoxyphenyl
11(1)	2-methylthio-benzyl	ethyl	bromomethyl	4-methoxyphenyl

Reference Example No.	R^1	R^2	$R^{3''}$	$R^{4'}$
11(2)	2-chloro-6-fluorobenzyl	ethyl	bromomethyl	4-methoxyphenyl
11(3)	2-chloro-6-fluorobenzyl	ethyl	bromomethyl	4-isobutoxyphenyl
12	2-methylthio-benzyl	ethyl	bromomethyl	4-propoxyphenyl
13	2-methylthio-benzyl	ethyl	methyl	4-(2-methoxyethyl)-phenyl
14	2-methylthio-benzyl	ethyl	bromomethyl	4-(2-methoxyethyl)-phenyl
15	2-methylthio-benzyl	ethyl	cyanomethyl	4-methoxyphenyl

Example 1

Production of ethyl 2,4(1H,3H)-dioxo-6-(4-methoxy-methoxyphenyl)-1-(2-methylthiobenzyl)-5-(methanesulfon-amidomethyl)thieno[2,3-d]pyrimidine-3-acetate:

To a suspension of sodium hydride (60% in oil; 60 mg, 1.5 mmol) in dimethylformamide (10 ml) was added the compound obtained in Reference Example 8 (0.6 g, 1.0 mmol) as well as methanesulfonamide (0.11 g, 1.2 mmol). The mixture was stirred at room temperature for 16 hours, at the end of which time it was concentrated. The residue was distributed between ethyl acetate and aqueous ammonium chloride solution and the aqueous layer was extracted with ethyl acetate. The extracts were combined, washed with NaCl-water, and dried ($MgSO_4$), and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography to provide a light-yellow amorphous solid (0.36 g, 59%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.33 (3H, t, J=7.1 Hz), 2.53 (3H, s), 2.88 (3H, s), 3.48 (3H, s), 4.28 (2H, q, J=7.1 Hz), 4.37 (2H, d, J=6.3 Hz), 4.85 (2H, s),

5.19 (2H, s), 5.36 (2H, s), 6.07 (1H, t), 7.0-7.20 (4H, m), 7.25-7.40 (4H, m).

Example 2

Production of ethyl 2,4(1H,3H)-dioxo-6-(4-methoxy-methoxyphenyl)-1-(2-methylthiobenzyl)-5-(benzenesulfon-amidomethyl)thieno[2,3-d]pyrimidine-3-acetate:

The compound obtained in Reference Example 8 (0.6 g) was reacted with benzenesulfonamide in lieu of methanesulfonamide in otherwise the same manner as Example 1 to provide a light-yellow amorphous solid (0.56 g, 83%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.34 (3H, t, J=7.1 Hz), 2.52 (3H, s), 3.50 (3H, s), 4.30 (2H, q, J=7.1 Hz), 4.27 (2H, m), 4.82 (2H, s), 5.21 (2H, s), 5.26 (2H, s), 6.63 (1H, t), 6.97 (1H, d), 7.08 (2H, d), 7.17 (1H, dt), 7.25-7.45 (6H, m), 7.51 (1H, t), 7.66 (2H, dd), 7.94 (1H, d).

Example 3

Using the compound obtained in Reference Example 8, 11, 12, 13 and 14, the similar procedure as in Example 1 was otherwise repeated to provide the following compounds. Compound 1: Ethyl 2,4(1H,3H)-dioxo-6-(4-methoxyphenyl)-1-(2-methylthiobenzyl)-5-(methanesulfonamidomethyl)thieno[2,3-d]pyrimidine-3-acetate. Yield 91%, amorphous.

Compound 2: Ethyl 2,4(1H,3H)-dioxo-6-(4-methoxyphenyl)-1-(2-chloro-6-fluorobenzyl)-5-(methanesulfonamidomethyl)thieno[2,3-d]pyrimidine-3-acetate. Yield 33%, amorphous.

Compound 3: Ethyl 2,4(1H,3H)-dioxo-6-(4-isobutoxyphenyl)-1-(2-chloro-6-fluorobenzyl)-5-(methanesulfonamidomethyl)thieno[2,3-d]pyrimidine-3-acetate. Yield 29%, amorphous.

Compound 4: Ethyl 2,4(1H,3H)-dioxo-6-(4-propoxyphenyl)-1-(2-methylthiobenzyl)-5-(methanesulfonamidomethyl)thieno[2,3-d]pyrimidine-3-

acetate. Yield 85%, amorphous.

Compound 5: Ethyl 2,4(1H,3H)-dioxo-6-(4-methoxymethoxy phenyl)-1-(2-methylthiobenzyl)-5-(ethanesulfonamidomethyl)thieno[2,3-d]pyrimidine-3-acetate. Yield 89%, m.p. 153-155°C.

Compound 6: Ethyl 2,4(1H,3H)-dioxo-6-(4-methoxymethoxy phenyl)-1-(2-methylthiobenzyl)-5-(propanesulfonamidomethyl)thieno[2,3-d]pyrimidine-3-acetate. Yield 85%, m.p. 122-123°C.

Compound 7: Ethyl 2,4(1H,3H)-dioxo-6-(4-propoxyphenyl)-1-(2-methylthiobenzyl)-5-(isopropanesulfonamidomethyl)thieno[2,3-d]pyrimidine-3-acetate. Yield 60%, amorphous.

Compound 8: Ethyl 2,4(1H,3H)-dioxo-6-(4-methoxymethoxy phenyl)-1-(2-methylthiobenzyl)-5-(trifluoromethanesulfonamidomethyl)thieno[2,3-d]pyrimidine-3-acetate. Yield 58%, amorphous.

Compound 9: Ethyl 2,4(1H,3H)-dioxo-6-(4-methoxymethoxy phenyl)-1-(2-methylthiobenzyl)-5-(isopropanesulfonamidomethyl)thieno[2,3-d]pyrimidine-3-acetate. Yield 93%, amorphous.

Compound 10: Ethyl 2,4(1H,3H)-dioxo-6-(4-propoxyphenyl)-1-(2-methylthiobenzyl)-5-(ethanesulfonamidomethyl)thieno[2,3-d]pyrimidine-3-acetate. Yield 84%, m.p. 132-134°C.

Compound 11: Ethyl 2,4(1H,3H)-dioxo-6-(4-(2-methoxyethyl)phenyl)-1-(2-methylthiobenzyl)-5-(methanesulfonamidomethyl)thieno[2,3-d]pyrimidine-3-acetate. Yield 59%, m.p. 131-134°C.

<u>Example 4</u>

<u>Production of ethyl 2,4(1H,3H)-dioxo-6-(4-methoxyphenyl)-1-(2-methylthiobenzyl)-5-(ethoxycarbonylmethyl)thieno[2,3-d]pyrimidine-3-acetate:</u>

The compound obtained in Reference Example 15 (0.11 g, 0.21 mmol) was dissolved in ethanol (20 ml)

followed by addition of saturated HCl-ethanol (10.5 N) (4 ml) and the mixture was refluxed for 48 hours. After cooling, the reaction mixture was distributed between ethyl acetate (50 ml) and saturated $NaHCO_3$-water (30 ml). The aqueous layer was re-extracted with ethyl acetate (30 ml). The extracts were combined, washed with NaCl-water, and dried ($MgSO_4$) and the solvent was distilled off under reduced pressure. The residue was crystallized from methanol to provide colorless crystals (0.10 g, 84%). m.p. 117-118°C.
Elemental analysis for $C_{29}H_{30}N_2O_7S \cdot 1/2H_2O$

	C (%)	H (%)	N (%)
Calcd.:	58.87;	5.28;	4.73
Found :	58.97;	5.25;	4.65

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.27 (3H, t, J=7.1 Hz), 1.29 (3H, t, J=7.1 Hz), 2.53 (3H, s), 3.82 (3H, s), 3.84 (2H, d), 4.19 (2H, q, J=7.0 Hz), 4.22 (2H, q, J=7.1 Hz), 4.82 (2H, s), 5.34 (2H, s), 6.89 (2H, d), 7.05 (1H, d), 7.15 (1H, t), 7.25 (2H, d), 7.32 (2H, t).

Example 5

Production of 2,4(1H,3H)-dioxo-6-(4-methoxymethoxyphenyl)-1-(2-methylthiobenzyl)-5-(methanesulfonamidomethyl)thieno[2,3-d]pyrimidine-3-aretic acid:

The compound obtained in Example 1 (0.5 g, 0.83 mmol) was dissolved in tetrahydrofuran (10 ml)-methanol (2 ml) followed by addition of 1N-sodium hydroxide-water (2 ml). This mixture was stirred at room temperature for 4 hours, after which 1N hydrochloric acid solution (2 ml) was added. The mixture was then concentrated and the residue was distributed between ethyl acetate and aqueous ammonium chloride solution. The aqueous layer was extracted with ethyl acetate. The extracts were combined, washed with NaCl-water, and dried ($MgSO_4$) and the solvent was distilled off under

reduced pressure. The residue was purified by silica gel column chromatography to give a light-yellow solid (0.55 g). This product was recrystallized from ethyl acetate-isopropyl ether to provide light-yellow crystals (0.40 g, 76%). m.p. 208-209°C.

Elemental analysis for $C_{26}H_{27}N_3O_8S_3 \cdot 1/2H_2O$

	C (%)	H (%)	N (%)
Calcd.:	50.80;	4.59;	6.83
Found :	50.75;	4.53;	6.79

^{1}H-NMR (300 MHz, DMSO) δ: 2.55 (3H, s), 2.87 (3H, s), 3.41 (3H, s), 4.30 (2H, s), 4.41 (2H, s), 5.21 (2H, s), 5.24 (2H, s), 6.91 (1H, t), 7.02 (1H, d), 7.11 (2H, d), 7.15 (1H, d), 7.33 (1H, t), 7.42 (2H, d).

Example 6

Production of ethyl 2,4(1H,3H)-dioxo-6-(4-isobutoxyphenyl)-1-(2-methylthiobenzyl)-5-(methanesulfonamidomethyl)thieno[2,3-d]pyrimidine-3-acetate:

To a solution of ethyl 2,4(1H,3H)-dioxo-6-(4-hydroxyphenyl)-1-(2-methylthiobenzyl)-5-(methanesulfonamidomethyl)thieno[2,3-d]pyrimidine-3-acetate (0.30 g), which was synthesized from ethyl 2,4(1H,3H)-dioxo-6-(4-methoxymethoxyphenyl)-1-(2-methylthiobenzyl)-5-(methanesulfonamidomethyl)thieno[2,3-d]pyrimidine-3-acetate (which was obtained in Example 1) with 1N hydrochloric acid in tetrahydrofuran at room temperature for 3 hours, in dimethylformamide (DMF) (25 ml) was added isobutyliodide (0.30 g) and K_2CO_3 (0.3 g). The mixture was stirred at room temperature for 24 hours. Then the mixture was evaporated in vacuo to give the residue, which was partitioned between ethyl acetate (50 ml) and aq.NH_4Cl (30 ml). The organic solution was dried with Na_2SO_4 and evaporated in vacuo to give a yellow amorphous, which was chromatographed on silica gel to provide a

yellow amorphous (0.11 g, 33%).

Example 7

Using the compounds obtained in Example 1, the similar procedure as in Example 6 is repeated to provide the following compounds:

Compound 1: Ethyl 2,4(1H,3H)-dioxo-6-(4-carboxymethoxyphenyl)-1-(2-methylthiobenzyl)-5-(methanesulfonamidomethyl)thieno[2,3-d]pyrimidine-3-acetate. Yield 70%, amorphous.

Compound 2: Ethyl 2,4(1H,3H)-dioxo-6-(4-allyloxyphenyl)-1-(2-methylthiobenzyl)-5-(methanesulfonamidomethyl)thieno[2,3-d]pyrimidine-3-acetate. Yield 84%, amorphous.

Compound 3: Ethyl 2,4(1H,3H)-dioxo-6-(4-butoxyphenyl)-1-(2-methylthiobenzyl)-5-(methanesulfonamidomethyl)thieno[2,3-d]pyrimidine-3-acetate. Yield 82%, amorphous.

Compound 4: Ethyl 2,4(1H,3H)-dioxo-5-[4-(2,2,2-trifluoroethoxyphanyl)]-1-(2-methylthiobenzyl)-5-(methanesulfonamidomethyl)thieno(2,3-d)pyrimidine-3-acetate.

Example 8

Production of ethyl 2,4(1H,3H)-dioxo-6-(4-methylamino carbonylmethoxyphenyl)-1-(2-methylthiobenzyl)-5-(methanesulfonamidomethyl)thieno [2,3-d]pyrimidine-3-acetate:

The compound 1 obtained in Example 7 was reacted with isobutylchloroformate and triethylamine in tetrahydrofuran (THF) at 0°C for three hours to provide acid anhydride compound, which was converted to amide derivative with methylamine. Yield 100%, amorphous.

Example 9

Using the compounds obtained in Example 7, the procedure as in Example 8 was repeated to produce the following compounds:

Compound 1: Ethyl 2,4(1H,3H)-dioxo-6-(4-

propylaminocarbonylmethoxyphenyl)-1-(2-methylthiobenzyl)-5-(methanesulfonamidomethyl)thieno[2,3-d]pyrimidine-3-acetate. Yield 95%, amorphous.
Compound 2: Ethyl 2,4(1H,3H)-dioxo-6-(4-piperazinecarbonylmethoxyphenyl)-1-(2-methylthiobenzyl)-5-(methanesulfonamidomethyl)thieno[2,3-d]pyrimidine-3-acetate. Yield 66%, amorphous.

Example 10

(1) Production of pivaloyloxymethyl 2,4(1H,3H)-dioxo-6-(4-methoxymethoxyphenyl)-1-(2-methylthiobenzyl)-5-(methanesulfonamidomethyl)-thieno[2,3-d]pyrimidine-3-acetate:

To an ice-cooled mixture of 2,4(1H,3H)-dioxo-5-methanesulfonamidomethyl-6-(4-methoxymethoxyphenyl)-1-(2-methylthiobenzyl)thieno[2,3-d]pyrimidine-3-acetic acid obtained in Example 5 (0.25 g, 0.413 mmol), K_2CO_3 (86 mg, 0.622 mmol) and KI (83 mg, 0.50 mmol) in DMF (8 ml) was added dropwise chloromethyl pivalate (72 ml, 0.50 mmol). After being stirred at 0°C to room temperature for 22 hours, the mixture was concentrated in vacuo and the residue was partitioned between ethyl acetate and brine. The aqueous phase was separated and extracted with ethyl acetate. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was subjected to silica gel column chromatography by eluting with ethyl acetate - hexane (4:6 - 1:1) to give the product (0.24 g, 80.8%) as a colorless syrup.

Crystallization from ethyl acetate-ether-hexane afforded the product (0.203 g, 72.6%) as white crystals. Yield 81%, m.p. 74-77°C.

(2) Employing the compound produced in Example 5 as the starting material, in accordance with substantially the same procedure as described the above item (1) of Example 10, the following compound is produced.
(R.S)-1-(cyclohexyloxycarbonyloxy)ethyl 2,4(1H,3H)-

dioxo-6-(4-methoxymethoxyphenyl)-1-(2-methylthiobenzyl)-5-(methanesulfonamidomethyl)thieno[2,3-d]pyrimidine-3-acetate

Example 11

Using the compounds obtained in Examples 2, 3, 4, 6, 7, 8 or 9, the procedure of Example 5 is otherwise repeated to provide the following compounds.

Compound 1: 2,4(1H,3H)-Dioxo-6-(4-methoxymethoxyphenyl)-1-(2-methylthiobenzyl)-5-(benzenesulfonamidomethyl)thieno[2,3-d]pyrimidine-3-acetic acid. Yield 68%, m.p. 120-125°C.

Compound 2: 2,4(1H,3H)-Dioxo-6-(4-methoxyphenyl)-1-(2-methylthiobenzyl)-5-(methanesulfonamidomethyl)-thieno[2,3-d]pyrimidine-3-acetic acid. Yield 76%, m.p. 208-209°C.

Compound 3: Ethyl 2,4(1H,3H)-dioxo-6-(4-methoxyphenyl)-1-(2-methylthiobenzyl)-5-(carboxylmethyl)thieno[2,3-d]-pyrimidine-3-acetate. Yield 65%, m.p. 243-245°C.

Compound 4: 2,4(1H,3H)-Dioxo-6-(4-methoxyphenyl)-1-(2-chloro-6-fluorobenzyl)-5-(methanesulfonamidomethyl)-thieno[2,3-d]pyrimidine-3-acetic acid. Yield 57%, amorphous.

Compound 5: 2,4(1H,3H)-Dioxo-6-(4-isobutoxyphenyl)-1-(2-chloro-6-fluorobenzyl)-5-(methanesulfonamidomethyl)-thieno[2,3-d]pyrimidine-3-acetic acid. Yield 30%, m.p. amorphous.

Compound 6: 2,4(1H,3H)-Dioxo-6-(4-isobutoxyphenyl)-1-(2-methylthiobenzyl)-5-(methanesulfonamidomethyl)-thieno[2,3-d]pyrimidine-3-acetic acid.

Compound 7: 2,4(1H,3H)-Dioxo-6-(4-propoxyphenyl)-1-(2-methylthiobenzyl)-5-(methanesulfonamidomethyl)-thieno[2,3-d]pyrimidine-3-acetic acid. Yield 84%, amorphous.

Compound 8: 2,4(1H,3H)-Dioxo-6-(4-butoxyphenyl)-1-(2-methylthiobenzyl)-5-(methanesulfonamidomethyl)-thieno[2,3-d]pyrimidine-3-acetic acid. Yield 85%,

amorphous.

Compound 9: 2,4(1H,3H)-Dioxo-6-(4-propoxyphenyl)-1-(2-methylthiobenzyl)-5-(ethanesulfonamidomethyl)-thieno[2,3-d]pyrimidine-3-acetic acid. amorphous.

Compound 10: 2,4(1H,3H)-Dioxo-6-(4-(2-methoxyethyl)phenyl)-1-(2-methylthiobenzyl)-5-(methanesulfonamidomethyl)thieno[2,3-d]pyrimidine-3-acetic acid. Yield 73%, m.p. 167-168°C.

Compound 11: 2,4(1H,3H)-Dioxo-6-(4-methoxymethoxy phenyl)-1-(2-methylthiobenzyl)-5-(isopropanesulfonamidomethyl)thieno[2,3-d]pyrimidine-3-acetic acid. Yield 64%, m.p. 112-114°C.

Compound 12: 2,4(1H,3H)-Dioxo-6-(4-methylaminocarbonyl-methoxyphenyl)-1-(2-methylthiobenzyl)-5-(methanesulfonamidomethyl)thieno[2,3-d]pyrimidine-3-acetic acid. Yield 58%, amorphous.

Compound 13: 2,4(1H,3H)-Dioxo-6-(4-propylamino carbonylmethoxyphenyl)-1-(2-methylthiobenzyl)-5-(methanesulfonamidomethyl)thieno[2,3-d]pyrimidine-3-acetic acid. Yield 81%, amorphous.

Compound 14: 2,4(1H,3H)-Dioxo-6-(4-piperazine carbonylmethoxyphenyl)-1-(2-methylthiobenzyl)-5-(methanesulfonamidomethyl)thieno[2,3-d]pyrimidine-3-acetic acid. Yield 84%, amorphous.

Compound 15: 2,4(1H,3H)-Dioxo-6-(4-propoxyphenyl)-1-(2-methylthiobenzyl)-5-(isopropanesulfonamidomethyl)-thieno[2,3-d]pyrimidine-3-acetic acid. Yield 84%, amorphous.

Compound 16: 2,4(1H,3H)-Dioxo-6-(4-methoxymethoxyphenyl)-1-(2-methylthiobenzyl)-5-(ethanesulfonamidomethyl)thieno[2,3-d]pyrimidine-3-acetic acid. Yield 80%, m.p. 125-128°C

Elemental analysis for $C_{27}H_{29}N_3O_8S_3 \cdot 1.0H_2O$

	C (%)	H (%)	N (%)
Calcd.:	50.85;	4.90;	6.59
Found :	51.15;	4.78;	6.54

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.33 (3H, t, J=7.4 Hz), 2.53 (3H, s), 2.96 (2H, q, J=7.4 Hz), 3.48 (3H, s), 4.35 (2H, d, J=6.6Hz), 4.92 (2H, s), 5.19 (2H, s), 5.36 (2H, s), 6.05 (1H, t, J=6.6 Hz), 7.01-7.37 (8H, m).

IR (KBr): 1702, 1649, 1543, 1487 cm^{-1}

Mass spectrum: 620.1 (MH^+)

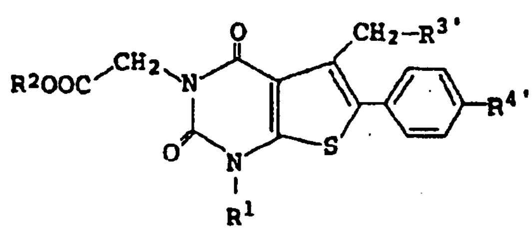
Compound 17: Ethyl 2,4(1H,3H)-dioxo-6-(4-methoxymethoxyphenyl)-1-(2-methylthiobenzyl)-5-(propanesulfonamidomethyl)thieno[2,3-d]pyrimidine-3-acetic acid. Yield 93%, m.p. 123-124°C

Compound 18: Ethyl 2,4(1H,3H)-dioxo-6-(4-methoxymethoxyphenyl)-1-(2-methylthiobenzyl)-5-(trifluoromethanesulfonamidomethyl)thieno[2,3-d]pyrimidine-3-acetic acid. Yield 52%, amorphous.

Compound 19: 2,4(1H,3H)-Dioxo-6-[4-(2,2,2-trifluoroethoxyphenyl)]-1-(2-methylthiobenzyl)-5-(methanesulfonamidomethyl)thieno[2,3-d]pyrimidine-3-acetic acid.

The compounds shown in the above Examples are listed in the Table 2.

Table 2



Example No.	R^1	R^2	$R^{3'}$	$R^{4'}$
1	2-methylthio-benzyl	ethyl	methane-sulfonamido	methoxymethoxy
2	2-m thylthio-benzyl	ethyl	benzene-sulfonamido	methoxymethoxy
3(1)	2-methylthio-benzyl	ethyl	methane-sulfonamido	methoxy

Example No.	R^1	R^2	$R^{3'}$	$R^{4'}$
3(2)	2-chloro-6-fluorobenzyl	ethyl	methane-sulfonamido	methoxy
3(3)	2-chloro-6-fluorobenzyl	ethyl	methane-sulfonamido	isobutoxy
3(4)	2-methylthio-benzyl	ethyl	methane-sulfonamido	propoxy
3(5)	2-methylthio-benzyl	ethyl	ethane-sulfonamido	methoxymethoxy
3(6)	2-methylthio-benzyl	ethyl	propane-sulfonamido	methoxymethoxy
3(7)	2-methylthio-benzyl	ethyl	isopropane-sulfonamido	propoxy
3(8)	2-methylthio-benzyl	ethyl	trifluoro-methane-sulfonamido	methoxymethoxy
3(9)	2-methylthio-benzyl	ethyl	isopropane-sulfonamido	methoxymethoxy
3(10)	2-methylthio-benzyl	ethyl	ethane-sulfonamido	propoxy
3(11)	2-methylthio-benzyl	ethyl	methane-sulfonamido	2-methoxyethyl
4	2-methylthio-benzyl	ethyl	ethoxy-carbonyl	methoxy
5	2-methylthio-benzyl	H	methane-sulfonamido	methoxymethoxy
6	2-methylthio-benzyl	ethyl	methane-sulfonamido	isobutoxy
7(1)	2-methylthio-benzyl	ethyl	methane-sulfonamido	carboxymethoxy
7(2)	2-methylthio-benzyl	ethyl	methane-sulfonamido	allyloxy
7(3)	2-methylthio-benzyl	ethyl	methane-sulfonamido	butoxy
7(4)	2-methylthio-benzyl	ethyl	methane-sulfonamido	2,2,2-trifluoro-ethoxy
8	2-methylthio-benzyl	ethyl	methane-sulfonamido	methylamino-carbonylmethoxy

Example No.	R^1	R^2	$R^{3'}$	$R^{4'}$
9(1)	2-methylthio-benzyl	ethyl	methane-sulfonamido	propylamino-carbonylmethoxy
9(2)	2-methylthio-benzyl	ethyl	methane-sulfonamido	piperazine-carbonylmethoxy
10(1)	2-methylthio-benzyl	pivaloyloxy-methyl	methane-sulfonamido	methoxymethoxy
10(2)	2-methylthio-benzyl	1-(cyclo-hexyloxy-carbonyloxy)-ethyl	methane-sulfonamido	methoxymethoxy
11(1)	2-methylthio-benzyl	H	benzen-sulfonamido	methoxymethoxy
11(2)	2-methylthio-benzyl	H	methane-sulfonamido	methoxy
11(3)	2-methylthio-benzyl	ethyl	carboxy	methoxy
11(4)	2-chloro-6-fluorobenzyl	H	methane-sulfonamido	methoxy
11(5)	2-chloro-6-fluorobenzyl	H	methane-sulfonamido	isobutoxy
11(6)	2-methylthio-benzyl	H	methane-sulfonamido	isobutoxy
11(7)	2-methylthio-benzyl	H	methane-sulfonamido	propoxy
11(8)	2-methylthio-benzyl	H	methane-sulfonamido	butoxy
11(9)	2-methylthio-benzyl	H	ethane-sulfonamido	propoxy
11(10)	2-methylthio-benzyl	H	methane-sulfonamido	2-methoxyethyl
11(11)	2-methylthio-benzyl	H	isopropane-sulfonamido	methoxymethoxy
11(12)	2-methylthio-benzyl	H	methane-sulfonamido	methylamino-carbonylmethoxy
11(13)	2-methylthio-benzyl	H	methane-sulfonamido	propylamino-carbonylmethoxy
11(14)	2-methylthio-benzyl	H	methane-sulfonamido	piperazine-carbonylmethoxy

Example No.	R^1	R^2	$R^{3'}$	$R^{4'}$
11(15)	2-methylthio-benzyl	H	isopropane-sulfonamide	propoxy
11(16)	2-methylthio-benzyl	H	ethane-sulfonamido	methoxymethoxy
11(17)	2-methylthio-benzyl	H	propane-sulfonamido	methoxymethoxy
11(18)	2-methylthio-benzyl	H	trifluoro-methane-sulfonamido	methoxymethoxy
11(19)	2-methylthio-benzyl	H	methane-sulfonamido	2,2,2-trifluoro-ethoxy

Example 12

A tablet is prepared by a conventional method using 100 mg of the compound produced in Example 1, 165 mg of lactose, 25 mg corn starch, 4 mg of polyvinyl alcohol and 1 mg of magnesium stearate.

Example 13

The compound (5 g) produced in Example 1 is dissolved in a distilled water for injection to make the total volume 100 ml. The solution is subjected to an aseptic filtration using a membrane filter of 0.22 micrometer (manufactured by Sumitomo Electric, Japan or by Saltorius, Germany). Each 2 ml of the filtrate is placed in a washed and sterilized vial and dried by freezing by a conventional method to prepare a freeze-dried injection of 100 mg/vial.

Example 14

A tablet is prepared by a conventional method using 100 mg of the compound produced in Example 5, 165 mg of lactose, 25 mg of corn starch, 4 mg of polyvinyl alcohol and 1 mg of magnesium stearate.

Example 15

The compound (5 g) produced in Example 5 is dissolved in a distilled water for injection to make

the total volume 100 ml. The solution is subjected to an aseptic filtration using a membrane filter of 0.22 micrometer (manufactured by Sumitomo Electric, Japan or by Saltorius, Germany). Each 2 ml of the filtrate is placed in a washed and sterilized vial and dried by freezing by a conventional method to prepare a freeze-dried injection of 100 mg/vial.

Example 16

A tablet is prepared by a conventional method using 100 mg of the compound (5) produced in Example 3, 165 mg of lactose, 25 mg of corn starch, 4 mg of polyvinyl alcohol and 1 mg of magnesium stearate.

Example 17

The compound (5) (5 g) produced in Example 3 was dissolved in a distilled water for injection to make the total volume 100 ml. The solution was subjected to an aseptic filtration using a membrane filter 0f 0.22 micrometer (manufactured by Sumitomo Electric, Japan or by Saltorius, Germany). Each 2 ml of the viltrate was placed in a washed and sterilized vial and dried by freezing to prepare a freeze-dried injection of 100 mg/vial.

Example 18

A tablet is prepared by a conventional method using 100 mg of the compound (16) produced in Example 11, 165 mg of lactose, 25 mg of corn starch, 4 mg of polyvinyl alcohol and 1 mg of magnesium stearate.

Example 19

The compound (16) (5 g) produced in Example 11 is dissolved in a distilled water for injection to make the total volume 100 ml. The solution is subjected to an aseptic filtration using a membrane filter of 0.22 micrometer (manufactured by Sumitomo Electric, Japan or by Saltorius, Germany). Each 2 ml of the filtrate is placed in a washed and sterilized vial and dried by freezing by a conventional method to prepare a freeze-

dried injection of 100 mg/vial.

Experimental Example 1

Binding Test to ET_A receptor expressed in CHO cell:

Procedure

cells: CHO cell expressing human ET_A 24 endothelin receptor, i.e. ET_A 24 cells

medium: DMEM 10% FCS Gln, nonessential amino acids, penicillin, streptomycin

Cells were seeded in 12 wells of 24 well plates at a density of $2x10^5$ cells/well (1 ml medium/well). On the next day, [^{3}H]arachidonic acid was added to each well to be 250 nCi(nanocurie)/ml. On the next day, the medium was sucked from the wells by the use of an aspirator to remove free arachidonic acid and floating cells, and then 0.5 ml of medium was added. This procedure was repeated again. After allowing to stand for 30 minutes in a CO_2 incubator, the medium was exchanged rapidly.

The sample of compound obtained in Example 5 or compound 16 of Example 11 was stepwise diluted with a buffer solution for dilution, containing $3.15x10^{-8}$M endothelin-1 (ET-1) {20 mM Tris, 5 mM $Mg(AcO)_2$, 2 mM EGTA, 0.03% NaN_3, 0.1% BSA, 0.05% CHAPS}. 10 µl of the solution was added to each well (final concentration of ET-1: $6.3x10^{-10}$M). The maximum reaction value was estimated by adding 10 µl of $3.15x10^{-8}$M ET-1. The radio activity under no stimulation was estimated by adding the buffer solution for dilution. After allowing to-stand for 30 minutes in the CO_2 incubator, the medium was completely collected and the radio activity of [^{3}H]arachidonic acid released in the medium was measured by a liquid scintillation counter. IC_{50} values were calculated by hill plot from the concentration and relative reaction value of each sample.

Abbreviations:

DMEM: Dulbecco's medified Eagle Medium

FCS : fetal calf serum

AcO : acetyloxy

EGTA: ethyleneglycol bis(2-aminoethyl-ether)tetraacetic acid

BSA : bovine serum albumin

CHAPS: 3-[(3-chloroamidopropyl)dimethyl-ammonio]-1-propanesulfonate

Results

IC_{50} values obtained are shown in Table 3:

[Table 3]

Test compound	IC_{50} value: μM
Compound obtained in Example 5	0.39 (n=2)
Compound 16 of Example 11	0.11 (n=2)

Experimental Example 2

Binding Test to ET_B receptor expressed in CHO cell:

Procedure

cells: CHO cell expressing human ET_B endothelin receptor, i.e. ET_B 12 cells

medium: DMEM 10% FCS Gln, nonessential amino acids, penicillin, streptomycin

Cells were seeded in 12 wells of 24 well plates at a density of $2x10^5$ cells/well (1 ml medium/well). On the next day, [^{3}H]arachidonic acid was added to each well to be 250 nCi(nanocurie)/ml. On the next day, the medium was sucked from the wells by the use of an aspirator to remove free arachidonic acid and floating cells, and then 0.5 ml of medium was added. This procedure was repeated agian. After allowing to stand for 30minutes in a CO_2 incubator, the medium was exchanged rapidly.

The sample of compound obtained in Example 5 or

compound 16 of Example 11 was stepwise diluted with a buffer solution for dilution, containing 3.15×10^{-8}M endothelin-1 (ET-1) {20 mM Tris, 5mM $Mg(AcO)_2$, 2 mM EGTA, 0.03% NaN_3, 0.1% BSA, 0.05% CHAPS}. 10 µl of the solution was added to each well (final concentration of ET-1: 6.3×10^{-10}M). The maximum reaction value was estimated by adding 10 µl of 3.15×10^{-8}M ET-1. The radio activity under no stimulation was estimated by adding the buffer solution for dilution. After allowing to-stand for 30 minutes in the CO_2 incubator, the medium was completely collected and the radio activity of [^{3}H]arachidonic acid released in the medium was measured by a liquid scintillation counter. IC_{50} values were calculated by Hill Plot from the concentration and relative reaction value of each sample.

Results

IC_{50} values obtained are shown in Table 4:

[Table 4]

Test compound	IC_{50} value: µM
Compound obtained in Example 5	0.49 (n=2)
Compound 16 of Example 11	0.13 (n=2)

Experimental Example 3

Inhibition Test on coronary artery where ET_A is expressed:

Procedure

3-mm ring samples for vehicle group and drug-treating group were prepared by removing fat and connective tissue from coronary artery enucleated from porcine heart and obtained from the adjacent portions thereof. The samples, hanging in Magnus tube filled with Krebs solution, were stabilized for 90 minutes under 2 g of static tension. After subjecting the

samples to constriction for 10 minutes by potassium chloride (KCl) (60 mM) to obtain the maximum reaction, the samples were then washed and stabilized for 60 minutes. After pre-treating compound obtained in Example 5 or Compound 16 of Example 11 or vehicle (H_2O) for 30 minutes, ET-1 (2 mM) was added to observe the maximum constriction.

The constriction efficiency (% KCl) of ET-1 was calculated as a relative value to KCl constriction of each sample which was regarded as 100%. Further, the inhibiting efficiency was calculated from the constriction efficiency of the drug-treating group calculated as a relative value to the constriction of the vehicle group which was regarded as 100%.

Results

The results are shown in Table 5.

[Table 5]

	% inhibition (MEAN ± S.E.M.)(n=) artery (ET-1 3nM)		Binding IC_{50} (μM)
Compound	0.1 μM	1 μM	ET_A
Compound in Example 5	7.6 ± 37.3 (3)	78.1 ± 11.9 (4)	0.0076
Compound 16 of Example 11	—	33.1 ± 8.6 (4)	0.0061

It is apparent from the results of Table 5 that in the ring samples of porcine coronary artery in which ET_A is expressed, the compounds of present invention suppress vascular (smooth muscle) constriction through the agonist of ET_A, i.e. ET-1 (3 nM).

Thus, it was confirmed that the compounds of present invention are antagonists for ET_A receptor.

Experimental Example 4

Inhibition Test on coronary vein where ET_B is expressed:

Procedure 1

3-mm ring samples for vehicle group and drug-treating group were prepared by removing fat and connective tissue from coronary vein enucleated from porcine heart and obtained from the adjacent portions thereof. The samples, hanging in Magnus tube filled with Krebs solution, were stabilized for 90 minutes under 0.5 g static tension. After subjecting the samples to constriction for 10 minutes by potassium chloride (KCl) (60 mM) to obtain the maximum reaction, the samples were washed and stabilized for 60 minutes. After pre-treating compound obtained in Example 5 or Compound 16 of Example 11 or vehicle (H_2O) for 30 minutes, S6c (1 nM) (S6c: sarafotoxin S6c, peptide type snake toxin consisting of 21 amino acids, it is useful for the selective agonist to ET_B receptor owing to the similarity of its structure to endothelin) was added to observe the maximum constriction.

The constriction efficiency (% KCl) of S6c was calculated as a relative value to KCl constriction of each sample which was regarded as 100%. Further, the inhibiting efficiency was calculated from the constriction efficiency of the drug-treating group calculated as a relative value to the constriction of the vehicle group which was regarded as 100%.

<u>Results</u>

The results are shown in Table 6.

[Table 6]

	% inhibition (MEAN ± S.E.M.) (n=) vein (S6c 1 nM)		Binding IC_{50} (μM)
Compound	0.1 μM	10 μM	ET_B
Compound in Example 5	73.4 ± 3.1 (3)	100 ± 0 (4)	0.100
Compound 16 of Example 11	53.3 ± 4.4 (4)	98.0 ± 1.1 (4)	0.054

It is apparent from the results of Table 6 that in

the ring samples of porcine coronary vein in which ET_B is expressed, the compounds of present invention suppress vascular (smooth muscle) constriction through the agonist of ET_B, i.e. S6c (1 nM).

Thus, it was confirmed that the compounds of present invention are antagonists for ET_B receptor.

Experimental Example 5

Binding Test to ET_A receptor expressed in an insect cell Sf9:

Procedure

Endothelin (ET) receptors were prepared by diluting fractions of insect cell (Sf9) membrane having human endothelin-A (ETA) receptors expressed, with an assay buffer {20 mM Tris-HCl, 2 mM EGTA (ethyleneglycol bls(2-aminoethylether) tetra acetic acid), 5 mM magnesium acetate, 0.1% BSA (bovine serum albumin), 0.03% NaN_3, 0.5 mM PMSF (phenyl methyl sulfonyl fluoride), 20 μg/ml leupeptin, 4 μg/ml E-64 (products of the Peptide Institute, Japan), 1 μg/ml pepstatin, (pH 7.2)} respectively in a concentration of 1.4 μg/ml in the former case and 0.7 μg/ml in the latte case.

To 100 μl of each portion was added 5 nM[^{125}I] endothelin-1 (2 μl). A dimethylsulfoxide solution (3 μl) of the test compound was added thereto and incubated at 25°C for 60 minutes.

And, to determine the maximum binding amount (B_0) and non-specific binding amount (NSB), lots to which a dimethyl sulfoxide solution (3 μl) or a dimethyl sulfoxide solution (3 μl) containing endothelin-1 (10^{-3}M) had been added, were also incubated.

These lots were supplemented with 0.05% CHAPS(3-[(3-chloroamidopropyl)dimethylammonio]-1-propanesulfonate)-assay buffer (1.5 ml), subjected to filtration through a glass fiber filter GF/F (trade name; product of Whatman Ltd. (England)), and then

washed with the same buffer (1.5 ml)).

Radioactivity on the filter was counted in a gamma-counter to determine the Percent Maximum Binding (PMB) in accordance with the aforesaid calculation formula. The concentration causing PMB=50% was determined as IC_{50} value. IC_{50} values of some of the compounds of this invention, synthesized in the above-mentioned examples, are shown in Table 7.

Table 7

Test compound (Compounds are shown by the Example No.)	IC_{50} value: μM Human endotherin-A receptor
5	0.011
potassium salt of 5	0.0076
11(7)	0.018
11(9)	0.015
11(11)	0.0066
11(15)	0.011
11(16)	0.0061
11(17)	0.022

According to the result shown in the Table 5, it has been proved that the compound or its salt of the present invention have excellent endothelin receptor antagonistic action to endothelin-B receptor.

<u>Experimental Example 6</u>

Binding Test to ET_B receptor expressed in an insect cell Sf9:

<u>Procedure</u>

Endothelin (ET) receptors were prepared by diluting fractions of insect cell (Sf9) membrane having human endothelin-B (ETB) receptors expressed, with an assay buffer {200 mM Tris-HCl, 2 mM EGTA

(ethylenegiycol bis(2-aminoethylether) tetra acetic acid), 5 mM magnesium acetate, 0.1% BSA (bovine serum albumin), 0.03% NaN_3, 0.5 mM PMSF(phenyl methyl sulfonyl fluoride), 20 μg/ml leupeptin, 4 μg/ml E-64 (products of the Peptide Institute), 1 μg/ml pepstatin, (pH 7.2)} respectively in a concentration of 1.4 μg/ml in the former case and 0.7 μg/ml in the latter case.

To 100 μl of each portion was added 5 nM[^{125}I] endothelin-1 (2 μl). A dimethylsulfoxide solution (3 μl) of the sample was added thereto and incubated at 25°C fpr 60 minutes.

And, to determine the maximum binding amount (B_0) and non-specific binding amount (NSB), lots to which a dimethyl sulfoxide solution (3 μl) or a dimethyl sulfoxide solution (3 μl) containing endothelin-1 (10^{-5}M) had been added, were also incubated.

These lots were supplemented with 0.05% CHAPS(3-[(3-chloroamidopropyl)dimethylammonio]-1-propanesulfonate)-assay buffer (1.5 ml), subjected to filtration through a glass fiber filter GF/F (trade name; product of Whatman Ltd. (England)), and then washed with the same buffer (1.5 ml).

Radioactivity on the filter was counted in a gamma-counter to determine the Percent Maximum Binding (PMB) in accordance with the aforesaid calculation formula. The concentration causing PMB=50% was determined as IC_{50} value. IC_{50} values of some of the compounds of this invention, synthesized in the above-mentioned examples, are shown in Table 8.

Table 8

Test compound (Compounds are shown by the Example No.)	IC_{50} value: μM Human endotherin-B receptor
5	0.20
potassium salt of 5	0.10
11(7)	0.22
11(9)	0.11
11(11)	0.090
11(15)	0.094
11(16)	0.054
11(17)	0.047

According to the result shown in the Table 6, it has been proved that the compound or its salt of the present invention have excellent endothelin receptor antagonistic action to endothelin-A receptor.

The potassium salt of the compound of the Working Example 5 was produced by employing the compound of the Working Example 5, potassium carbonate and water-ethanol in a conventional manner.

Industrial Applicability

The thienopyrimidine derivative of the present invention possesses outstanding endothelin receptor antagonist activity and, therefore, the endothelin antagonist composition containing this thienopyrimidine derivative in accordance with the invention can be used with advantage as a prophylactic or therapeutic drug for acute renal failure, myocardial infarction, liver disorder, angina pectoris, cerebral infarction, cerebrovasospasm, hypertension, kidney disease, asthma, ectopic angina, Rayneau syndrome, pulmonary

hypertension, surgical shock, chronic heart failure, atherosclerosis, cardiac hypertrophy, migrane, etc., as a prophylactic or therapeutic drug for organ surgery- or graft-associated hypofunction of organs, or as a prophylactic drug for vascular restenosis following percutaneous transluminal coronary angioplasty (PTCA), or as an inhibitor for vasoconstriction of coronary artery, coronary vein, cerebrovascular system or pulmonary vascular system.

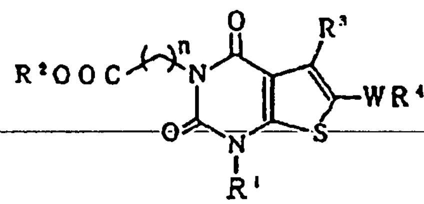
CLAIMS

What we claim is:

1. A thieno[2,3-d]pyrimidine derivative, wherein the thienopyrimidine derivative has (1) a carboxyl group or an ester thereof and (2) a group other than a carboxyl group which is capable of forming an anion or a group convertible thereinto in its molecule.

2. A compound according to claim 1, wherein the group which is capable of forming anion or a group convertible thereinto other than a carboxyl group is tetrazolyl, an optionally substituted sulfonamido group, a phosphono group or a sulfo group, each of which may optionally be substituted by alkyl or acyl.

3. A compound of the formula:



wherein each of R^1 and R^2 are hydrogen or an optionally substituted hydrocarbon residue, R^3 is a C_{1-6} alkyl group which is substituted by a C_{1-6} alkoxy-carbonyl group or a group of the formula: $-NH-SO_2-R^5$, wherein R^5 is (1) a C_{1-6} alkyl group which may optionally be substituted by halogen or (2) a C_{6-14} aryl group, R^4 is an optionally substituted hydrocarbon residue or an optionally substituted heterocyclic group, W denotes a chemical bond or a spacer group and n denotes an integer of 1 to 3; or a salt thereof.

4. A compound according to claim 3, wherein R^1 is an optionally substituted C_{1-20} hydrocarbon residue.

5. A compound according to claim 4, wherein the C_{1-20} hydrocarbon residue is a C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{2-10} alkenyl, C_{6-14} aryl or C_{7-20} aralkyl group.

6. A compound according to claim 4, wherein R^1 is an optionally substituted C_{7-20} aralkyl group.

7. A compound according to claim 3, wherein R^1 is a hydrocarbon residue optionally substituted with (1) halogen, (2) nitro, (3) cyano, (4) an optionally substituted hydroxyl group, (5) a group of the formula: $-S(O)f-R^6$, wherein f denotes an integer of 0 to 2, and R^6 is a hydrogen atom or an optionally substituted hydrocarbon residue, (6) an optionally substituted amino group or (7) an optionally substituted 5- or 6-membered heterocyclic group which contains 1 to 4 heteroatom(s) of oxygen, sulfur or nitrogen.

8. A compound according to claim 3, wherein R^1 is a hydrocarbon residue optionally substituted with halogen or a C_{1-4} alkylthio group.

9. A compound according to claim 3, wherein R^2 is an optionally substituted C_{1-20} hydrocarbon residue.

10. A compound according to claim 9, wherein R^2 is an optionally substituted C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{2-10} alkenyl, C_{6-14} aryl or C_{7-20} aralkyl group.

11. A compound according to claim 3, wherein R^2 is an optionally substituted C_{1-10} alkyl.

12. A compound according to claim 3, wherein R^2 is a hydrocarbon residue optionally substituted with (1) halogen, (2) nitro, (3) cyano, (4) an optionally substituted hydroxyl group, (5) a group of the formula: $-S(O)f-R^6$, wherein f denotes an integer of 0 to 2, and R^6 is a hydrogen atom or an optionally substituted hydrocarbon residue, (6) an optionally substituted amino group or (7) an optionally substituted 5- or 6-membered heterocyclic group which contains 1 to 4 heteroatom(s) of oxygen, sulfur or nitrogen.

13. A compound according to claim 3, wherein R^2 is a hydrocarbon residue optionally substituted with (1) halogen, (2) nitro, (3) hydroxyl, (4) cyano, (5) C_{1-4}

alkylthio, (6) C_{1-4} alkoxy, (7) C_{1-6} alkyl-carbonyloxy or (8) C_{3-6} cycloalkyl-oxycarbonyl.

14. A compound according to claim 3, wherein R^2 is hydrogen or a C_{1-6} alkyl group which may be optionally substituted by C_{1-6} alkyl-carbonyloxy or C_{3-6} cycloalkyl-oxycarbonyl oxy.

15. A compound according to claim 3, wherein R^3 is a C_{1-6} alkyl group which is substituted by a C_{1-6} alkoxy-carbonyl group or a group of the formula: $-NH-SO_2-R^{5'}$, wherein $R^{5'}$ is a C_{1-6} alkyl group or a C_{6-14} aryl group.

16. A compound according to claim 3, wherein R^3 is a C_{1-6} alkyl group which is substituted by a group of the formula: $-NH-SO_2-R^5$, wherein R^5 is (1) a C_{1-6} alkyl group which may optionally be substituted by halogen or (2) a C_{6-14} aryl group.

17. A compound according to claim 3, wherein R^3 is a C_{1-6} alkyl group which is substituted by a group of the formula: $-NH-SO_2-R^{5'}$, wherein $R^{5'}$ is a C_{1-6} alkyl group or a C_{6-14} aryl group.

18. A compound according to claim 3, wherein R^4 is an optionally substituted C_{1-20} hydrocarbon residue or an optionally substituted 5- to 13-membered heterocyclic group which contains 1 to 4 heteroatom(s) of oxygen, sulfur or nitrogen.

19. A compound according to claim 3, wherein the R^4 is an optionally substituted C_{6-14} aryl group.

20. A compound according to claim 3, wherein R^4 is a hydrocarbon residue optionally substituted with (1) halogen, (2) nitro, (3) cyano, (4) C_{1-6} alkoxy which may optionally be substituted by C_{1-6} alkoxy, carboxyl, halogen, C_{1-6} alkyl-carbamoyl or 5 to 7 membered nitrogen-containing heterocyclic group-carbonyl, (5) C_{7-13} aralkyloxy, (6) C_{1-4} alkyl which may be substituted by C_{1-3} alkoxy, (7) C_{1-6} alkanoyl, (8) C_{1-4} alkylthio, (9)

C_{2-6} alkenyloxy, (10) C_{1-6} alkoxy-carbonyl or (11) C_{1-6} alkyl-carbamoyl.

21. A compound according to claim 3, wherein R^4 is a hydrocarbon residue optionally substituted with C_{1-6} alkoxy which may optionally be substituted by C_{1-6} alkoxy, carboxyl, halogen, C_{1-6} alkyl-carbamoyl or a 5 to 7 membered nitrogen-containing heterocyclic group-carbonyl.

22. A compound according to claim 3, wherein W is a spacer group selected from the group consisting of (1) C_{1-4} alkylene, (2) C_{2-6} alkenylene, (3) a group of the formula $-(CH_2)cNR^{10}-$, where c represents an integer of 0-3, R^{10} represents hydrogen or C_{1-6} alkyl, (4) -CO-, (5) a group of the formula $-CONR^{10}-$, where R^{10} is as defined above, (6) -O-, (7) a group of the formula: -S(O)f-, where f represents an integer of 0 to 2, and (8) a group of the formula: $-NR^{10}S(O)e-$, where e represents an integer of 0-2; R^{10} is as defined above.

23. A compound according to claim 3, wherein W is a chemical bond.

24. A compound according to claim 3, wherein R^1 is a benzyl group which may optionally be substituted by (1) halogen or (2) C_{1-4} alkylthio,

R^2 is a hydrogen atom or a C_{1-4} alkyl group which may optionally be substituted by (1) C_{1-6} alkyl-carbonyloxy or (2) C_{3-6} cycloalkyl-oxycarbonyloxy,

R^3 is a C_{1-6} alkyl group which is substituted by (1) a C_{1-6} alkoxy-carbonyl group or (2) a group of the formula: $-NH-SO_2-R^{5''}$ (wherein $R^{5''}$ is (1) a C_{1-3} alkyl group which may optionally be substituted by halogen or (2) a phenyl group,

R^4 is a phenyl group which is substituted by (1) C_{1-4} alkoxy which may be substituted by C_{1-6} alkoxy, carboxyl, C_{1-6} alkyl-carbamoyl, piperazinecarbonyl or

halogen, (2) C_{7-8} aralkyloxy, (3) C_{1-4} alkyl which may be substituted by C_{1-3} alkoxy, (4) C_{1-6} alkanoyl, (5) C_{2-4} alkenyloxy, (6) C_{1-6} alkoxy-carbonyl or (7) C_{1-6} carbamoyl.

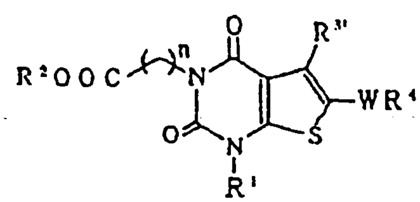
25. 2,4(1H,3H)-dioxo-6-(4-methoxymethoxyphenyl)-1-(2-methylthiobenzyl)-5-(methanesulfonamidomethyl)-thieno[2,3-d]pyrimidine-3-acetic acid or its salt.

26. 2,4(1H,3H)-dioxo-6-(4-methoxymethoxyphenyl)-1-(2-methylthiobenzyl)-5-(ethanesulfonamidomethyl)-thieno[2,3-d]pyrimidine-3-acetic acid or its salt.

27. 2,4(1H,3H)-dioxo-6-(4-methoxyphenyl)-1-(2-methylthiobenzyl)-5-(mthanesulfonamidomethyl)-thieno[2,3-d]pyrimidine-3-acetic acid or its salt.

28. Ethyl 2,4(1H,3H)-dioxo-6-(4-methoxyphenyl)-1-(2-methylthiobenzyl)-5-(carboxymethyl)thieno[2,3-d]pyrimidine-3-acetate.

29. A method for producing a compound as defined in claim 3, which comprises subjecting a compound of the formula:



wherein, R^1, R^2, W and R^4 have the same meaning as defined in claim 3 and $R^{3'}$ is a C_{1-6} alkyl group which is halogenated or cyanated, to (1) a nucleophilic substitution reaction with a sulfonamide compound when the alkyl of $R^{3'}$ is halogenated or (2) alkali-hydrolysis and then esterification when the alkyl of $R^{3'}$ is cyanated.

30. A pharmaceutical composition, which comprises a compound as defined in claim 1, 3 or 28 and a carrier, excipient or diluent therefor.

31. A pharmaceutical composition according to claim 30, which is a therapeutic drug for treating

vasoconstriction in a mammal.

32. A pharmaceutical composition according to claim 31, wherein the vasoconstriction is in a coronary artery, coronary vein, cerebrovascular system or pulmonary vascular system.

33. A pharmaceutical composition according to claim 30, which is for antagonizing endothelin activity.

34. A pharmaceutical composition according to claim 33, which is a therapeutic drug for acute renal insufficiency, cardiac infarction or liver insufficiency.

35. A pharmaceutical composition according to claim 33, which is a treapeutic drug for hypofunction of an organ caused by a surgery or transplant.

36. A pharmaceutical composition according to claim 35, wherein the organ is liver.

37. A method for treating a mammal suffering from vasoconstriction, which comprises administering an effective amount of a compound as defined in claim 1, 3 or 28 to the mammal.

38. A method for treating a mammal suffering from acute renal insufficiency, cardiac infarction or liver insufficiency, which comprises administering an effective amount of a compound as defined in claim 1, 3 or 28 to the mammal.

39. Use of a compound as defined in claim 1, 3 or 28 for producing a pharmaceutical composition for the manufacture of a medicament for therapeutic application on vasoconstriction.

40. Use of a compound as defined in claim 1, 3 or 28 for producing a pharmaceutical composition for the manufacture of a medicament for therapeutic application on acute renal insufficiency, cardiac infarction or liver insufficiency.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/JP 96/02290

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D495/04 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 640 606 A (TAKEDA CHEMICAL INDUSTRIES, LTD.) 1 March 1995 cited in the application see claims	1-3,30, 33
A	WO 93 08799 A (SMITHKLINE BEECHAM CORPORATION) 13 May 1993 cited in the application see claims	1-3,30, 33

[ ] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
16 December 1996	20.12.1996

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Van Bijlen, H

INTERNATIONAL SEARCH REPORT

I national application No.
PCT/JP 96/02290

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 37 and 38 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. al Application No
PCT/JP 96/02290

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-640606	01-03-95	CA-A-	2130859	27-02-95
		CN-A-	1106663	16-08-95
		FI-A-	943912	05-06-95
		HU-A-	71116	28-11-95
		JP-A-	8073467	19-03-96
		NO-A-	943146	27-02-95
		FI-A-	950021	30-12-95
WO-A-9308799	13-05-93	AP-A-	433	17-11-95
		AU-B-	669866	27-06-96
		AU-A-	3125993	07-06-93
		BG-A-	98752	31-05-95
		BR-A-	9206722	18-07-95
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		CZ-A-	9401109	18-01-95
		EP-A-	0612244	31-08-94
		FI-A-	942059	04-07-94
		HU-A-	67665	28-04-95
		JP-T-	7501322	09-02-95
		NO-A-	941650	01-07-94
		NZ-A-	245000	28-05-96
		OA-A-	9921	15-08-94
		PT-A-	101038	28-02-94
		SK-A-	52194	08-03-95
		ZA-A-	9208467	05-05-93